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: SAFE-PEDRUG research consortium (safepedrug.eu)

Transparency Register ID number (for organisations): _____

Country: Belgium _____

E-mail address: info@safepedrug.eu _____

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

- X 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
- X Academia or a research or educational institute
- ○ A public authority
- ○ Other (please specify)

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
- X 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?

We agree that the Paediatric Regulation has the potential to have a substantial impact on the development of paediatric medicines. As we will mention below, we encounter some gaps within the current version of the legislation but in general we agree that this specific legislation has stimulated the consideration of paediatric drug development by pharmaceutical companies, academia and regulatory authorities. Moreover, it has provoked a better collaboration between stakeholders and resulted in a more harmonised and global approach of paediatric drug development.

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?

The focus for new drugs is on the adult market, which is - unfortunately - also reflected in the drugs that are covered by a paediatric investigation plan (PIP). Most of the PIPs are performed in endocrinology, oncology, infectious diseases, and cardiovascular diseases, which relates to the associated economic importance in the adult market. Additionally, we see that PIPs focus on adult indication, more than on the specific paediatric indications. Moreover, long term follow-up studies are hardly included in the PIP. Therefore, we would like to request for more post marketing studies in the paediatric population (cf. the growth hormone database (KIGS-registry)). Furthermore, despite the Paediatric Regulation, new paediatric labelled drugs still lack data concerning their use in specific paediatric populations (such as children with significant comorbidities and/or with comedications, critically ill children, obese children, etc).

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?

It is not possible for us to judge whether the number of new paediatric medicines that are availability in EU Member States has increased. In fact, we want to draw the attention to the problem of withdrawal of drugs or formulations from the market and the problem of temporary shortages of drugs that are frequently used in children. We definitely need age-appropriate formulations on the market, which is not always the case now, despite a previously agreed PIP with an age-appropriate formulation. An appropriate drug formulation is the starting point of an efficient drug therapy for children. The unavailability of appropriate formulations often results in drug manipulation by parents and care givers and in extratemporaneous preparation or compounding by the pharmacist. If compounding or manipulation is likely to be required, then data related to this should at least be generated by industry and proven to be safe and efficacious for its intended use, as well as approved by competent authorities and provided in the Summary of Product Characteristics. As an example, in Belgium we do not have an age-appropriate formulation of an ACE-inhibitor while this was one of the drug classes that were evaluated in children through the paediatric medicine initiatives.

Even though new licensed treatments have made it to the market, it is sometimes difficult to replace existing medications in view of the difficulty to change old habits in the clinic and of the fact that prices of newer treatments may be substantially higher than for existing (currently off-label) therapies.

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?

The costs for pharmaceutical companies to comply with an agreed paediatric investigation plan are reasonable when the extension of the supplementary protection certificate (SPC) can result in a significant financial incentive through the drug consumption for adults. However, paediatric labelling should be a driving force on its own. We ask for a better incentive for paediatric use. This could be achieved by means of an independent paediatric patent or by a better price setting for paediatric formulations and applications, etc.
Furthermore, we think that we can make the paediatric evaluation process more (cost) efficient. This can be achieved by using more full and partial extrapolation approaches through the use modelling and simulation techniques and by more targeted research applying juvenile animal models that provide information on both target organ toxicity and developmental effects. This could lead to an optimised trial design, more optimal and less burdensome blood sampling schemes and the inclusion of fewer children, while still maintaining the information content of the trial.

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?

Cf. 2.4.

2.6. The orphan reward

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

Figures show that the orphan reward is not attractive for pharmaceutical companies. The reward/incentive needs reconsideration.

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?

EMA and its PDCO has adapted the implementation during the previous years and some early problems have been solved by early interaction meetings, review of the class waiver list, teleconference with FDA to strive for alignment between recommendation from different authorities, etc. Despite these efforts, some paediatric clinical trials still run the risk to be extra complicated due to differing expectations of EMA and FDA.
The attitude of pharmaceutical companies to the Paediatric Regulation has changed during the previous years too. Paediatric drug development has become part of the drug development strategy and companies have started to think earlier about the potential for a paediatric indication.
The inclusion of adolescents in adult trials could be interesting for some drugs. In our opinion, there cannot be a general rule for this; this should be considered case-by-case.

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?

We agree that the 'mechanism of action' is promising. The possibility of a mandatory approach should be considered. However, we want to emphasize that the 'mechanism of action' principle can only be applied when thoroughly evaluated in preclinical testing.

2.9. Deferrals

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

This top-down approach from adult to child leads to considerable delays in making medicines available to children. In our opinion, we should invest in model-based approaches that can help to increase prior knowledge on paediatric use before the adult trials have been completed. This can be achieved by applying modelling and simulation techniques (either population PK(PD) of PBPK) more broadly and by developing predictive paediatric animal models.
We think that pharmaceutical companies should be stimulated more to complete the paediatric trials within the time frame of the adult drug development, i.e. before the marketing authorisation of a drug. Clinical trials before market authorisation tend to be small and provide a very limited safety database. The unique risk for long term adverse developmental effects can hence not adequately be addressed before market authorisation of the product. This will imply post marketing studies to guarantee long term follow-up, and may well be the optimal approach to evaluate long-term risks for the developing child.

2.10. Voluntary paediatric investigation plans

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

Voluntary paediatric investigation plans will only be performed if there is a valuable 'paediatric' incentive for doing this.
Partnerships between industry and academia (public-private partnerships) may increase the number of voluntary paediatric investigation plans, preferably for off-patent drugs, off-knowledge drugs or for drugs that should be evaluated for neglected diseases. Academia should play a pivotal role in the task prioritisation of these research consortia.

2.11. Biosimilars

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

In order to receive a paediatric labelling, drug evaluation for a biosimilar should include bioequivalence studies (both PK and PD) in children. In addition, safety registries should be part of the paediatric drug evaluation process for biosimilars.

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?

Figures show that the PUMA concept resulted in only three PUMA-labelled drugs, which is a disappointment. The fact that prescribers can continue to prescribe cheaper off-label competitor drugs with the same active ingredient is a big obstacle to the PUMA concept. As stated above, we think that public-private partnerships can improve investments in the paediatric evaluation of off-patent drugs.

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?

Head-to-head trials could improve our knowledge on labelled drugs. Unfortunately, such trials are not encouraged or required by the Paediatric Regulation.
As to the topic of recruitment problems, we ask for a fair compensation for parents of participating patients (travel cost, cost of not working, etc).
We want to draw the attention to drugs that are evaluated in developing countries (through a PIP) but are not available in these countries once these drugs are approved. Such issues will need proper attention too.

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?

We suggest that the central PDCO group would be assisted by multidisciplinary clinical expert panels (including paediatric specialists, clinical pharmacologists, clinical pharmacists, research pharmacists, and research nurses). Through such an approach, the central group could guarantee uniformity and a correct implementation of the legislation, and the expert panels would give their specialised advise on the PIP. This construction requires extra budget that could come from a 'PIP-fee'.

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?

As stated above, we need more research in the paediatric population, that also encompasses neonates, younger age groups (e.g. also for immunological diseases), obese children, children with comorbidities, critically ill children, etc. Not only after the adult development of a drug is almost finished, but also more in parallel time-wise and for indications not yet studied in adults.

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?

Promising techniques for the future of paediatric pharmacology will be PBPK, PKPD modelling and simulation and juvenile animal models. Besides, we will have to invest in early development of age-appropriate formulations and administration tools, as appropriate.

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?

Both regulations (Paediatric regulation and orphan regulation) are not complementary as they have different targets: the paediatric regulation is mainly focusing on blockbusters (on the adult market), the orphan regulation focuses on rare diseases. The incentive of both should be paediatric labelling, which should be financially attractive for pharmaceutical companies.