

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: __BfArM_____

Transparency Register ID number (for organisations): _____

Country: _____Germany_____

E-mail address: _____paediatric@bfarm.de_____

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

- My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication
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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
- Academia or a research or educational institute
- A public authority
- Other (please specify)

A

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
- 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. The Paediatric Regulation is necessary to guarantee the paediatric population timely access to new, innovative medication, which might otherwise only be developed for adults. This is also evidenced by the fact that for applications with a product specific waiver request often lower than requested age cut offs or even no waiver at all are accepted by the PDCO. This indicates that without specific legislations developments especially in the younger age subsets might be forgone.

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?

As the starting point for the paediatric investigation plan is the adult condition, a disproportional high number of PIPs concern the development in diseases which occur more often in adults than in children, e.g. type 2 diabetes. With this regard developments mainly have to be expected in areas which are of major interest to the adult population because higher revenue can be expected here, while fields of major paediatric interest, e.g. neonatology are neglected in comparison. This surely is a shortfall of the Paediatric Regulation. On the other hand, there certainly are areas where children have profited. As detailed in the EMA 10-year report treatment of JIA is an example here.

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?

No comment.

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?

Costs occurring during pharmaceutical development are as of now highly intransparent, including the costs of PIPs.

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?

Early, strategic planning surely is paramount and it has to be noted that a rather high number of PIPs are still submitted late compared to the timelines provided in the Paediatric Regulation. This certainly hampers a timely completion of the program.

In some cases the program conducted for the paediatric population deviates from the one agreed in the PIP opinion. In these cases, modifications with a request to retrospectively align the program with the PIP opinion are submitted. In order not to block the applicant from submitting a MAA or subject children to more studies, a positive opinion is often granted, although, the actual program might be sub-optimal compared to the one which has been agreed before in the PIP opinion. In addition, the number of PIPs that need to be conducted varies between substances depending on the number of conditions which are investigated in adults. If a company has several PIPs for one substance the burden is obviously higher.

Of note, the transparency of successful paediatric developments awarded the paediatric rewards should be improved, also with respect to the paediatric reward for orphan medicinal products. An easily identifiable document which refers to the data on which the reward was based would increase awareness of the type of requirements and may therefore help to stimulate further development. Allowing to search for products authorised in children (exclusively or mixed with adult indication) on the EMA website or for products for which the market exclusivity has been prolonged would be highly welcome.

2.6. The orphan reward

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

No comment.

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?

The Regulation's implementation has certainly improved as all parties involved have gained experience. From a NCA's point of view the timely submission is paramount in order to guarantee a timely completion of the program. With this regard the generous granting of deferrals should be carefully considered as it has become apparent that deferrals can complicate the timely conduct of paediatric studies. It might be helpful to discuss the Paediatric Regulation in relation to the Clinical Trials Regulation as far as the need for a PIP (if appropriate) in order to obtain a clinical trial authorisation is concerned. In many cases paediatric clinical studies have already been started at the time of PIP submission. In these cases, modifications to the on-going studies are often not possible resulting in the need to conduct additional studies and endangering a timely completion of the development program and therefore the possibility for the MAH to receive the reward.

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?

As the paediatric program is currently subject to the chosen adult condition, there are certainly some missed opportunities for example in the field of oncology or neonatology where developments for diseases specific for the paediatric population might have been missed. A MOA based approach strictly focussing on paediatric areas with particularly high need might be a way out here.

2.9. Deferrals

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

Yes, we generally agree. It might be useful to review the deferral policy. While long deferrals might not considerably improve the safety of the subjects in paediatric studies, they can significantly increase recruitment issues if the product is already available on the market and also promote off-label use.

2.10. Voluntary paediatric investigation plans

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

So far the experience with voluntary measures, be it the development of PUMAs or studies in response to the paediatric needs lists, have been rather disappointing. Voluntary PIPs as described in the consultation document might be a tool to directly address specific sponsors, which might increase the chance for a positive response. This approach might also provide valuable input from other stakeholders, thereby improving the ability to respond to the actual paediatric needs. In the end, the impact of such an approach will most likely be dependent on the reward which can be obtained if the requested data is provided.

2.11. Biosimilars

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

From our point of view the measures provided in the Paediatric Regulation generally are sufficient. No PIP requesting paediatric data is needed for biosimilars as results can be extrapolated to the paediatric population. Due to the complexity of the active substance and the manufacturing process and the regulatory requirements, the development of biosimilars is already a rather long and costly procedure. We have observed that special paediatric formulations/strengths are sometimes not developed. This may be due to the usually small paediatric market where considerable revenues

cannot be expected, which is a problem that is difficult to address.

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?

The PUMA concept certainly did not meet the expectations. The number of off-patent products which are used off-label in children is still high. These products are available on the market. The amount and quality of the paediatric data available for these compounds is variable, which implies that the programs which would be needed in order to obtain a marketing authorization are also diverse. In a number of cases the efforts will not be negligible. The problem is complex and although several attempts have been made, there does not seem to be a clear and easy solution. It is questionable, if a national approach would be able to increase the number of PUMAs and fulfil the goal to grant all children in the EU access to licensed off-patent products.

Since the orphan legislation is also open to off-patent products, the market exclusivity provided by the orphan legislation may be an alternative incentive for rare diseases in children.

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?

One major benefit of the Paediatric Regulation is that it has changed the attitude towards paediatric trials. While some time ago clinical trials in children have been regarded as unethical, nowadays it is accepted that these trials can and need to be done to grant children access to medicinal products that have shown to be efficacious and safe in their age group. A paediatric patient in a clinical trial is under much better surveillance than a patient who receives a medicinal product off-label, which mitigates the risk. Experience with the paediatric regulation has also led to discussions and knowledge on study designs which are possible in this population and concepts for modelling, simulation and extrapolation if a complete program is not feasible. In addition, age appropriate formulations which also can benefit certain sub-groups of the adult population have been developed and acceptability has been tested. All this has and will further improve the availability of safe and efficacious medication for the paediatric population and also result in new input for adult programs.

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?

The lack of re-imburement for the assessment of PIPs and affiliated procedures is certainly a problem and this approach has put an additional burden on the NCAs. This is also reflected in the number of vacant PDCO seats. Re-imburement could enable the NCAs to direct further resources to the field regulator field of paediatrics which could be beneficial to all parties involved.

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?

One major achievement of the Paediatric Regulation is that it changed the mind-set towards paediatric clinical trials. While this research has been seen as unethical some time ago, nowadays well-designed clinical trials are seen as a necessity. The increasing number of paediatric programs has led to more experience with age appropriate formulations, trial designs, end-points and also with regard to recruitment issues. Insight has also been gained on fields where recruitment is especially challenging and where different approaches might need to be applied. Nevertheless basic knowledge on several fields (e.g. ontogenetic aspects of drug metabolism or the natural history of certain diseases), which could benefit a number of development programs is still insufficient.

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?

Generally as the Paediatric Regulation is based on the adult development programs, the adult trends as described in the consultation document will probably be followed. However, the programs requested might change as new concepts, e.g. extrapolation and modelling-base approaches are developed. Close collaboration between all concerned parties including HTAs is deemed necessary in order to grant the paediatric population timely access to these medications.

Another trend might be multi-arm, multi-company trials as described for Gaucher disease (document EMA/44410/2014) this approach might facilitate programs in rare disease with high scientific interest and many candidate products.

As an aside, it has been noticed that a number of products are only planned for development in second line indications in the adult populations, although the compound might also be beneficial as a first line treatment and off-label use is likely. While this is a minor problem as regards the paediatric population, because the PDCO can request a first-line development under the same condition if needed, this might lead to the rather unusual situation of off-label use in the adult population in the first line indication while the product is licensed for this indication in the paediatric population.

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?

A major problem is the late submission of the PIPs. This leads to delays in the paediatric programs. Often deferrals are granted in order not to block the submission of a MA for the adult population,

because these programs are often close to completion. If the marketing authorisation in the adult population is granted and the product is available on the market, paediatric recruitment gets much more difficult and the product is used off-label in the paediatric population which creates problems of its own. With this regard the deferral policy might need to be re-discussed. Another major issue is the fact, that modifications are often submitted retrospectively and somehow sub-optimal approaches generating only reduced paediatric data have to be accepted, because otherwise whole paediatric studies would have to be repeated which is often deemed to be unethical and leads to further delays.