

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: vfa_____

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Please indicate whether you are replying as:

- A citizen
- A business
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- A patient group
- A healthcare professional organisation
- Academia or a research or educational institute
- public authority
- Other (please specify)

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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?

Yes. We have a positive example with the Orphan Medicines Regulation which has effected a lot of orphan medicines being developed and marketed. The same effect we are seeing in the field of paediatric medicines, where more and more medicinal products have been meanwhile approved for the paediatric population.

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 Paediatric Medicines Regulation has contributed that medicines for the paediatric population have been developed and approved, especially in the following indications:

- Infectious diseases, such as HIV, HCV, fungal or bacterial infections
- Rheumatologic diseases
- Hypertension
- Hypercholesterolaemia
- Orphan diseases including rare paediatric cancers
- PAH
- Plaque-psoriasis
- Diabetes
- Asthma
- Epilepsy

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 Have existing treatments been replaced by new licensed treatments?

The number of new paediatric medicines per year including extensions of the age range is highly variable reaching from a low in 2010 (only 13) to a high in 2009 and 2015 (30) as it is the case for all new medicines (2010: only 21; 2015: 50).

Since 2013 there have been on average 23 new paediatric medicines approvals per year. In 2016 there were 28 and for 2017 we expect far more. Thus, we see a tendency towards increasing numbers of paediatric medicines.

All of these paediatric approvals are valuable since they will offer appropriately tested first-time or alternative treatments for minors and thus help to reduce off-label-use.

Yet, we see a growing gap between approval and use of the paediatric medicines due to the HTA processes in the individual member states which in most cases are not taking into account the special conditions for paediatric development. This is expected to result in withdrawals from the market when companies need to fulfil the same requirements for rare paediatric indications as for large adult indications (full HTA dossiers that are almost as extensive as marketing authorisation applications), see also 2.4. In addition extrapolation data instead of results from randomised clinical trials is a concept that is meanwhile well accepted for paediatric development by the PDCO, but often leads to negative HTA-assessments.

For PUMA products it has been observed that compounded products or generic adult medicines were prescribed despite the availability of paediatric medicines.

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 the companies are substantial and are not limited to one or two clinical trials:

It begins with the drafting of the PIP which is often a time- and resource-demanding task. To find incidence rates of adult indications in children is complex and requires expertise that companies often do not have in-house. Already in this phase experts need to be consulted. Every 5th to 6th PIP requires the development of an additional age-appropriate strength or even an age-appropriate dosage form. And given the fact that you need a lot of clinical trial sites which often recruit only a few children paediatric trials are more resource-consuming and longer lasting than trials with adults.

And after paediatric approval at least in Germany the companies have to compile a very complex dossier for the HTA even if the paediatric extension is only for 10 or 20 children per year in Germany.

vfa therefore believes that the € 20 million per PIP is an underestimation of paediatric development costs.

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?

With regard to the fact that around 45 % of the companies fail to benefit from the reward system vfa sees room for improvement. Many PIPs – at least in the first 5-7 years after introduction of the Paediatric Regulation – were so demanding that a timely finalisation to get the SPC prolongation was not possible.

Companies choosing the decentralised procedure are in disadvantage. On one hand these medicines may not be intended for all European countries from the beginning, e.g. because of divergent medical practice and on the other hand because some countries fail to comply with the timelines.

2.6. The orphan reward

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

The orphan reward is helpful in cases where no or insufficient patent protection of the active ingredient exists. Where a company will be able to get the SPC reward it will prefer this option. We have seen only three orphans where companies have chosen and got the two-year extension of market exclusivity.

Therefore the orphan reward is valuable and should be kept in spite of being seen by many companies only as second choice.

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?

Yes. In general this is true e.g. with the more flexible handling of the submission timepoint, the acceptance of modelling and extrapolation and with splitting of PIPs.
There are a few exemptions:

The concept for PIPs for paediatric-only products should be revised to limit the shared information to the amount that would be necessary for a scientific advice.

There should be sources made publicly available for the generation of evidence that the incidence of a certain indication is too low to conduct clinical trials. This may reduce the burden for companies to prove the feasibility of trials.

A mechanism for multiple drug developments in one indication ("waves of development ") needs to be installed. This may include a general deferral for some indications and an assessment of a group of products by PDCO (see also 2.9).

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?

vfa holds the opinion that the current approach – i.e. to apply the concept of mechanism of action on a voluntary basis – is adequate and should be kept.

Any additional research may be of interest for the society but should then also be financed via public funds. In particular SMEs might be overburdened due to financial constraints to conduct the research themselves.

2.9. Deferrals

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

Yes, vfa agrees with this assessment. Given that minors are vulnerable subjects and that ethics committees must apply high ethical standards to the protection of these trial participants the current approach regarding deferrals preventing too early testing is justified.

Deferrals should be assessed further for multiple developments for one indication where companies initiate trials in parallel ("waves of development "). This competition leads to slow recruitment or even to trials that ultimately cannot be finalised. This situation is not ethical. Whereas the interest in new drugs for life-threatening diseases is indeed justified, the inclusion of children in trials which cannot be finalised should be avoided.

2.10. Voluntary paediatric investigation plans

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

No, vfa agrees with this analysis that companies may submit voluntary PIPs which also entitle for an incentive.

2.11. Biosimilars

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

For ethical reasons – minimising paediatric studies – the current approach is adequate. However, to safeguard the availability of age-appropriate formulations also generics and biosimilars should be required to develop age appropriate formulations and put them on the market. Due to cost constraints originator products may not be reimbursed any longer or companies may choose to withdraw them from the market when only generic prices are reimbursed.

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?

vfa agrees that the PUMA concept has failed, since over the last 10 years only 3 PUMAs have been approved. This mainly due to the fact that the incentive is not sufficient, especially since the use of PUMA medicines is systematically reduced by the continuous use of cheaper non-approved pharmacy-made preparations and/or by off-label-use of medicines with the same ingredient. As long as the payers reimburse these non-approved medicines there will be no solution of this problem.

In addition, excessive requirements regarding PIPs for PUMAs in the first years have contributed to the low interest of companies. And the research-based companies were and are fully booked with paediatric research for innovative medicines.

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?

vfa agrees with this analysis. Such problems are not restricted to diabetes type II but also are true for multiple sclerosis or asthma. Perhaps the currently running IMI projects INNODIA for Diabetes type 1 or the current project for creation of a pan-European paediatric clinical trials network could bring some solutions.

Deferrals might be another option to group the products in these development waves and assess all products together for a better coordination of the requested trials and to avoid overlapping trial populations. Collaboration might be easier in a later stage of development or once the products have been authorised for adults.

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?

vfa holds the opinion that not all tasks of the regulatory agencies should be financed by industry. Paediatrics is one field where the society has an interest and therefore taxpayers' money should come into play.

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?

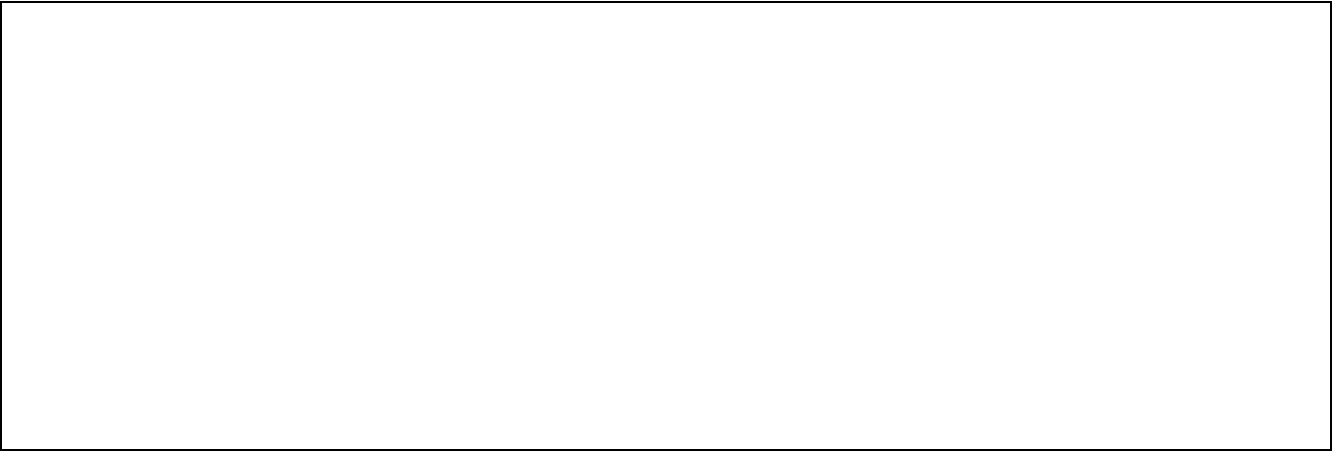
Whereas in some European countries there are regional or national networks of paediatric research sites there is still a need to build a network in Europe. Hopefully this will be achieved by the current IMI2 project creating a pan-European paediatric clinical trials network and the IMI project of creating a comprehensive 'paediatric preclinical POC platform' to enable clinical molecule development for children with cancer.

Complementary to these initiatives the work of EnprEMA should be further supported and additional support for paediatric networks should be provided.

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?

Regarding precision (or personalised) medicine: Of course, children should also benefit from such medicines in case the correspondent disease is also affecting children, as this is e.g. already the case for Abacavir or Ataluren.



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?

Overall the Paediatric Regulation has effected that paediatric development is an integrated part of the R&D for new medicines.

Whereas the approval of paediatric medicines works, problems with HTA are arising. The lack of specific HTA-mechanisms for paediatric indications jeopardises the access of children to these medicines and which are difficult to resolve.