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: Austrian Medicines & Medical Devices Agency

Transparency Register ID number (for organisations): _____

Country: Austria

E-mail address: basg-paediatrics@ages.at

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
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- o I do not agree that my contribution will be published at all

Please indicate whether you are replying as:

- o A citizen
- o A business
- o A non-governmental organisation (NGO)
- o An industry association
- o A patient group
- o A healthcare professional organisation
- o Academia or a research or educational institute
- X A public authority
- o Other (please specify)

If you are a business, please indicate the size of your business

- o Self-employed
- o Micro-enterprise (under 10 employees)
- o Small enterprise (under 50 employees)
- o Medium-sized enterprise (under 250 employees)
- o Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- o Local
- X National
- o Across several countries
- X EU
- X 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?
supported

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?
Mainly innovative areas with new medicines like biologics, oncology, several niche areas and orphan indications The legislation also has facilitated more general approaches on drug development, relevant for children, e.g. specific dosing requirements, formulation, requirement to address relevant clinical end points, approaches for extrapolation of information from source data, where evidence based data generation is more feasible, 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?

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?

Average cost over 10 years is not an appropriate indicator. Industry has extensively increased expertise and knowledge how to address paediatric development, consequently current average annual costs should have dropped substantially from 10 years ago.

The representativeness of this external study is limited, as it is based only on Companies contributing data.

Average cost also does not take into account large variability of these costs depending on the product. Factors contributing to this could include availability of patients in total and in the paediatric age range, how innovative a product is (new products will require a more extensive development program) etc.

Development costs are not always clearly assignable to the paediatric population, eg. endpoints agreed in PIPs are often more pragmatic, better reflecting clinical relevant outcomes and could support adult R/B, paediatric formulations could be of benefit also to adult (e.g. more convenient, more accurate dosing possible, easier to swallow also for handicapped patients…)

One cost factory that could be reduced is due to the fact that at the time when submitting a PIP (after availability of first PK data), a full discussion of the development is premature, but already requires a lot of efforts from the industry side – often plans subsequently need modifications or in some cases or development is discontinued. It would be more appropriate if legislation would allow a step-wise evolvement of the PIP during development. The early discussion could then focus on envisaged waivers and deferrals, but would not necessarily contain all studies including detailed key binding elements

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?

Especially in rarer diseases this might not be sufficient. The reward does not at all take into account to which extent paediatric needs are covered by the new medicine. Other approached could address this. An adult medicinal product with a large market where a PIP would cover a very small additional paediatric subpopulation currently gets the same SPC as a drug that is mainly developed for a paediatric indication.

The argument that a surplus in reward could cover the costs of discontinued PIPs would only be applicable to large companies with a large pipeline. Many small companies do not have the option to compensate for such risks. The current Paed Reg also does not allow to limit PIP requirements for such SMEs. Specific funding could be one option to compensate for this.

No option to link efforts in a PIP to the level of reward. In some cases even a meta-analysis or an extrapolation approach only would generate the same reward as a complete development program as requested in other PIPs.

National payers in some cases do not respect that a licensed e.g. paediatric formulation is actually the one that should be reimbursed and insist on using a cheaper adult dosage form (i.e they reimburse off label use only).

2.6. The orphan reward

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

In principle the Company has the option between different rewards which makes this system flexible to enhance attractiveness for orphan drug developers by choosing the economically more attractive option. This seems fair and is supported.

One problem might be that the ODD has to be confirmed at the initial MA. If a paediatric development is deferred, this would imply that initial MA this is not based on paediatric data. Options could be considered to postpone ODD confirmation, if a substantial proportion of patients with the condition are in the paediatric age range and the PIP completion is deferred.

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?

Especially larger Companies have learned how to appropriately include a paediatric development program into their product pipelines.

Especially smaller companies and Companies based outside of the EU are sometimes still not sufficiently informed about the EU legal requirements.

One important aspects not mentioned above is the increase of paediatric only scientific advices or the option to include paediatric specific aspects into a broader scientific advice request. As these procedures are coordinated between PDCO and SAWP, the outcome is likely to be agreeable to both PDCO and CHMP. Companies increasingly use this option for support. (Data??)
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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?

The use of the term waiver is sometimes misleadingly used. Often in the sense of waiving a PIP measure rather than the correct waiving of a target population/condition. For unfeasible measures alternate approaches should be considered based on which a later R/B assessment and MA could be performed.

2.9. Deferrals

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

Also here definition and legal basis are sometimes unclear. The legal term is only focusing on the initial MAA time point. A more stepwise developed time schedule (based on upcoming evidence) might be more appropriate. Unclear legal grounds, e.g. in paediatric only developments or conditional MA, where discussion what would be acceptable as postmarketing commitments is by definition outside PIP measures and hence raises reluctance of PDCO to defer these. This would need a closer link to discussions with CHMP and PRAC on such measures.

It is difficult to find (prospectively) a balance between available data and decision to start recruiting children – deferral time lines are granted or denied before much safety or efficacy data are available.

2.10. Voluntary paediatric investigation plans

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

Voluntary PIPs are something that we are not aware of, unless within the context of a PUMA (see comments below). Our impression is that PIPs submissions where not legally required (e.g. for hybrid applications) are rather due to insufficient awareness of the legal obligations by the companies and not driven by strategic considerations.

2.11. Biosimilars

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

Compare above. Often the paediatric development is deferred, leaving an even shorter window for the originator to get payed back for these efforts. One option to compensate this could be specific data protection periods for the deferred paediatric development (e.g. similar to the one granted for PUMAs).

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?

As also evident from the rather limited use of this option the PUMA apparently in many cases lacks attractiveness. This might also be due to the often quite challenging requests what PDCO want to see in such cases (e.g. initially the whole paediatric age range had to be covered, this has been clarified in the meantime).

One problem might be that the reward is identical no matter how much efforts are required to fulfil this PIP. Also – many such PIPs are for paediatric formulations - which would be often welcomed – however, there is no guarantee that the licensed product will be reimbursed, which would make such a development useless for a company.

Data protection is difficult to enforce legally. E.g. how could an originator company prevent, that generics/biosimilar products are prescribed in children if the scientific evidence should be equally applicable.

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?

In principle agree to most comments above. The upcoming Clinical Trial Legislation might help to find approaches agreeable in all member states compared to now.

Reluctance of companies to collaborate (e.g. in a head to head comparison of upcoming medicinal products). This is not only logistics and recruitment related. There is no appropriate regulatory framework for such an approach. How would an active controlled trial PIP be agreed on, which company would be response for compliance for which key binding elements? CHMP also would not request such comparative data. How would the inferior arm product be handled at CHMP?

Another problem in this context: there is currently no option to actively invite a Company back for rediscussion of their agreed PIP
e.g. if similar products have e.g. raised safety issues
when scientific evidence would require some changes (e.g. another more accepted endpoint)
a clearly more promising product is in the pipeline (especially in rare conditions)
another product has been licensed and covers some more paediatric needs
such actively requested modifications might have to foresee some compensation for already made efforts

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?

This clearly already has an impact, as even some of the large NCA have limited their activities in the PDCO. Some MS do not have any delegate, several no alternate. Attendance is limited to only one member, the number of procedures allowed to be taken by the delegates is limited.

A compensation system (e.g. similar to COMP/SAWP procedures) would be needed. Therefore the PDCO activities have been included in the data gathering exercise. After the review of the Fee Reg. hopefully there are fees for all the paediatric activities.

A similar problem is with regard to Paediatric only Scientific Advice requests. Also these NCA have to volunteer. As no compensation can be expected for these, NCA often discourage SAWP delegates to take these resulting in problems assigning such procedures. This could be solved by redistributing incoming fees for other SA procedures evenly or as above for COMP by compensation form the EU commission side.

Data gathering, has to be included in the update of Fee Regulation.

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?

There is clearly more commitment to performing paediatric research now. This is not limited to trials requested within agreed PIPs. But the requirements as defined in the Paediatric Regulation have triggered discussion to find solutions how to generate data in paediatrics. There is clearly a broad increase of available expertise that developed as a result of these requirements.

Also ethical aspects (including children in clinical trials or not?) have seen a paradigm shift towards generating scientific evidence as a consequence of such discussions.

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?

Agree to most of these comments.

Options for a more flexible procedure to discuss PIs would often help to come up with a more tailored approach to different development programs. This could include, more than one clock-stop, e.g. also to trigger specific interaction with other committees or working parties (e.g. CAT, PRAC, SAWP, CHMP) to subsequently come up with a consolidated outcome.

As mentioned above, e.g. in conditional MA (also the legal base for adaptive pathway) the PIP approach is not fully applicable, as by definition the PIP ends at the initial MA. This would need more coordinated efforts to agree on such a program between involved committees/working parties. Formally post-marketing key binding elements as the tool in a PIP would have to be aligned with measures requested in a RMP. Currently this is exclusively in the mandate of different committees.

EMA is currently working on implementing (SPOR) (currently on iteration 1 for the PMS). In this iteration no details on paediatric information is foreseen. These aspects should be implemented as soon as possible.

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?

The Paed Reg resulted in clearly raising awareness of this previously neglected area to generate evidence to make medicinal products available in children.

However, the current procedure with regard to many details is driven too much by legal obligations that are not always ensuring scientifically optimal progress.

Some suggestions:

- The 60+60 day procedure is too unflexible, not allowing for an adequate and tailored discussion of many relevant points
- The focus on an initial agreement on the full development at the end of phase 1 results in a high number of subsequent modifications, a more stepwise agreement on details at later stages would be preferable. The details required in the initial PIP (e.g. study design, sample size, ebndpoint….) at the end of phase 1 are scientifically often not yet justifiable (often not even correct), but required, but it has been argued that they are necessary as otherwise it would be unclear what measures are actually deferred.
- There should be an option to postpone important discussions (e.g. on much later performed confirmatory trials to a time where the scientific basis is available)
- There should be an option to request revision of an agreed PIP (e.g. by actively reinviting a Company to rediscuss or by a routinely requested revision procedure to make sure a former PIP agreed is still scientifically in accordance with current standards/needs, e.g every 2 years or prior to start the Ph3 in children)
- There is currently an automatic requirement for NCAs in each member state to issue a compliance statement to implement the compliance check, even if the MHA does not need it (e.g. patent expired already). This could be limited to cases, where the MHA requests issuing such a compliance statement.