

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: German Pharmaceutical Industry Association

Transparency Register ID number (for organisations): 76399831150-89

Country: Germany

E-mail address: pserrano@bpi.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)

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

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, the German Pharmaceutical Industry Association (BPI) agrees that a specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines.

There are only few medications available for children and adolescents in many indications, or none at all.

Medical professionals and parents often have no choice but to use preparations which are only approved for adults. "Off-label use" on children of medicinal products which have been approved for adults only, i.e. use outside of the actual approval, has become common practice.

The legislation should help to significantly reduce the extent of this practice.

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?

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?

From the point of view of medicinal products based on proven substances, for which the concept of the Paediatric Use Marketing Authorisation (PUMA) was conceived, the number of new paediatric medicines available in Member States hasn't increased. Since the regulation came onto effect, only three medicinal products were granted with PUMA.

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?

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?

2.6. The orphan reward

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

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?

Regarding the Paediatric Use Marketing Authorisation the Regulation's implementation clearly hasn't improved. The problems haven't been solved yet.

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?

Application form Part A: Request for Waiver(s)

According to the current application form Part A information should be provided for each condition and / indication:

Request for (a) Waiver(s) *Information about waiver should be provided for each condition and /or indication*

Condition: |

However, the application form doesn't provide the possibility to request a waiver for a selected indication under "condition", but it's only possible to specify one waiver for the whole condition. The praxis showed, that conditions with several indications exist, for which only single indications shall be requested to be waived (This was possible in the previous versions of the Part A form).

Proposal for solution: The application form should be adjusted properly.

2.9. Deferrals

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

2.10. Voluntary paediatric investigation plans

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

2.11. Biosimilars

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

Doctors should be allowed to prescribe what on basis of scientific data they consider to be the most suitable medicinal products for patients. They should not have to make fundamental decisions on treatment because of economic or market regulatory constraints. The focus must be on the safety and efficacy of treatment.

The biopharmaceutical (reference product or biosimilar) prescribed by a doctor must not be substituted *aut idem* for another product. Another biopharmaceutical may only be substituted during treatment on the order of the doctor in charge and previous intense discussion, consultation and agreement with the patient.

In order to prevent substitution and replacement and to clearly classify the biopharmaceuticals given to a patient, the prescription of biological medicinal products (reference product or biosimilar) must be based on the brand names of the active substances.

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?

No, the PUMA concept is not a disappointment. However, the output clearly is a disappointment, having being granted only three PUMA so far.

This type of marketing authorisation was introduced in order to counteract the worrisome use of active ingredients on children which are not meant for paediatric use (off-label use). There is a clear advantage in supplying the paediatric population with safe and effective medicinal products which have been proved for newborns, children and adolescents.

- Data and marketing protection in connection with a PUMA does not keep medicinal products with the same active ingredient which have been approved for adults from being marketed and prescribed for children and adolescents. Off-label use of these medicinal products has often become established practice in paediatric medicine. Consequently, both physicians and patients have become "accustomed" to off-label use of certain products.
- The studies of paediatric use which are conducted in the course of obtaining the PUMA may in some cases confirm and support off-label use of competing medicinal products; in other words, PUMA studies may be used to support off-label use, contrary to their intended purpose.

- Because of the studies which have to be conducted, PUMA medicinal products are often hardly able to compete in terms of price with medicinal products with established off-label use, which are often available as generics.
- Physicians are likely to have little interest in abandoning proven off-label use of inexpensive medicinal products in favour of medicinal products which have the same active ingredients but are more expensive (European Commission 2013b); this is all the more true when they are promoted to do so by the health care system.

These aspects, especially the problem of off-label use, are cited in the available publications of the EMA and the European Commission, as well as the opinions of European associations concerning the public consultation, as a decisive criterion for the PUMA's lack of success.

The resulting disadvantages for the affected manufacturers are not offset by the data and marketing protection periods. Data exclusivity is an ineffective instrument in a market characterized by substitution. This protection merely prevents competitors from marketing the same active ingredient as a medicinal product for paediatric use, or for the same indication, but does not hinder the presence in the market of medicinal products for adults with the same active ingredient. Other responses submitted in the course of the Commission's public consultation process point out that national reimbursement systems sometimes favour or even require off-label use. In a generic competitive environment, off-label use can therefore be seen as a key factor in the PUMA's lack of success.

The presence of an added benefit should be acknowledged for all PUMA products given that products in off-label use have been converted into approved paediatric medicinal products.

Data Exclusivity should be complemented with Market Exclusivity. This would protect medicinal products with PUMA from market competition with similar medicines with similar indications once they are approved and would offer an new incentive for the development of medicinal products for children.

A prohibition on substitution should be introduced for paediatric medicinal products: otherwise approved paediatric medications will continue to be replaced by standard medications which are not approved for 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?

Recruitment of subjects for clinical trials:

1. Recruitment of paediatric subjects for clinical trials is often difficult for SMEs (including e.g. orphan drugs as product group), if big pharmaceutical companies have already approved PIPs for big studies in the same indication which is then considered by PDCO as being the standard.

Example: Roche clinical trial for high-grade glioma (orphan disease) with Avastin, 82 study center worldwide, 123 subjects (NCT01390948). Such a number of centers for a paediatric trial with e.g. an Advanced Therapy Medicinal Product (ATMP) is not affordable for an SME and providing IMP to centers distributed worldwide cannot be performed due to manufacturing reasons. However, PDCO requested comparable study designs (Randomised Controlled Studies, RCT) as are performed by big pharmaceutical companies with already approved PIPs in this indication.

Proposal for solution:

Acceptance of one treatment arm with historical controls with a comparable study design.

2. Another example can be given by paediatric trials with allergen products for specific immunotherapy where many products have to undergo a full clinical development program to get a marketing authorisation (MA). The MA application must contain the results of the trials that were conducted according to an approved Paediatric Investigational Plan (PIP). To fulfill this requirement a Standard-PIP has been established, providing guidance in the performance of clinical trials for allergen products for specific immunotherapy. This guidance describes the necessity to conduct double-blind, placebo-controlled (DBPC) trials over a period of 5 years (3 years of treatment plus 2 years treatment-free follow-up).

A clinical trial was planned by a company in six countries with 70-80 study centers and 600 patients to be randomized, including 200 adolescents over a period of six years.

Since the recruitment of 1/3 adolescents could not be reached the following activities were undertaken:

- Prolongation increase of recruitment period by 1 year
- Involvement of a specific paediatric study group in Germany
 - 58 sites contacted -> 2 sites participated
 - 2 adolescents randomized
- e-Diary use extended to tablet PCs and smart phones

Nevertheless, only 49 adolescents could be randomized.

Currently, after 3 years of treatment 534 patients incl. 46 adolescents are still in the study.

Non-recruitment of adolescents was mainly due to ethical reasons:

- Withdrawing a patient from an active treatment over 5 years while he/she is supposed to be most susceptible is considered unethical by physicians and even more by parents
- Long-term setting interferes with the personal situation of adolescents
- Motivation for 5 years of seasonal e-Diary completion is hard

This is not the only company that has to perform long-term clinical trials in children and adolescents with allergen products for specific immunotherapy, since due to a special regulation in Germany (Therapy allergens ordinance – Therapieallergeneverordnung) all companies are forced to conduct such trials for their products falling under this regulation in the foreseeable future.

Thus, the requirements of the current Standard-PIP for SIT products seems too unrealistic to be achieved. Recruiting adolescents is worse than recruiting adults, but recruiting children for the same study design will be even worse than the recruitment of adolescents.

Proposal for solution:

Please reconsider the current Standard-PIP concerning the requirement of a 5 years study in children. An option could be a PAES documenting safety data under controlled conditions.

Since studies with allergen therapies very often suffer from confounder s.a. polysensitization or variable pollen exposure not provoking symptoms to be differentiated from placebo positive results in specific subgroups (s.a. regional, mono-sensitized or others) should be considered for extrapolation.

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?

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?

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?

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?

Paediatric Investigation Plan (PIP):

1. Application form (Part A) of PIP

is not appropriate for Advanced Therapy Medicinal Products, e.g. dosages: Amount of cells per dosage should be possible. Further problems exist when submitting information regarding strength and excipients.

Proposal for solution: The application form should be adjusted properly, taking into consideration the particularities of ATMPs (e.g. by giving the possibility to add free text for the dosage).

2. Point in time of PIP-submission

According to Article 16, Paediatric Regulation (EC) No 1901/2006, the PIP or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults. However, this requirement is far too early, since normally not even data from proof-of-concept studies in adults can be provided at this stage.

Proposal for solution: Submission should be required not before data of a planned Phase II are available.

3. Line extensions for patent-protected products

A problem arises in the fact, that it's not sufficient to submit a PIP for the extensions (e.g. new dosage form or indication) only. A PIP should also comprise already approved dosage forms, which results in a multitude of clinical studies, even though the products already have a marketing authorization, at least in parts.

Proposal for solution: It should be possible to submit a PIP for the Line Extension only.