

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 Initiative “Better Medicines for Children” (IKAM)

Transparency Register ID number (for organisations): 092766824500-05

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- A healthcare professional organisation
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- 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

- o 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?

In general, the development of adequate paediatric medicines with an evidence-based meaning cannot be stipulated by legislation alone. The delivery of proof for evidence will not come from the developers but from those, prescribing, administering and observing patients. It needs the scientific guided collection of information on the, positive or negative, treatment of patients. This will add to the drug safety information, the marketing authorisation holders are collecting.

Therefore it needs the support of academic or governmental collection systems, so called registries. But on a guided, harmonized basis, to make the collected data comparable and robust. Also the creation and maintenance of such collection tools to gain knowledge on evidence could be triggered by national or European common legislative content. This would include the collection of information on the so-called Off-label Use, a difficult project as we try to move out of this “grey zone” of paediatric treatment with the EU Paediatric Regulation (EUPR) since 10 years.

This concept of collecting treatment knowledge to support statements on evidence will come up against borders in certain areas of paediatric drug treatment. For sure, it needs adapted concepts in certain areas like pediatric intensive care, neonatology, or Pediatric oncology (PO). Because of long development phases for oncologic drugs in combination with high risk drug substances, therapies in PO are nearly regular developed off-label by systematically testing adult chemotherapeutic compounds in children.

On the other hand, the acceptance of such data by the authorities could be encouraged by adequate legal supportive measures. As far as common acceptance criteria are agreeable by (hopefully) all national competent authorities, this would support the voluntary development of new or the improvement of existing medicines for children.

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?

Looking from a regulatory perspective, a paediatric drug is available as soon as the medicinal product is authorised for its use. But this does not reflect reality. The drug is often available sooner, as the drug substance with its known use in a certain treatment is already on the market as an adult drug. So at this time it is available and healthcare professionals will prescribe or administer it. The fact, that the paediatric treatment is not available doesn't mean that the substance is not used in children (key word: off-label use).

It is crucial that the lawgiver, European and national, encourage the development of authorised

paediatric indications. But it needs also the awareness of social and economic thinking of marketing authorisation holders for or against decisions supporting the paediatric development on a voluntary basis.

The official statement of paediatric needs is a good basis and acts as a clue for paediatric development. For new drugs with new substances but even more for existing drugs and their improvement.

As conclusion, the EUPR worked quite well for the development of paediatric indications with new substances. On the other hand, the extension of existing therapies for paediatric needs didn't work quite well. 3 PUMAs compared to the existing mass of marketing authorisations combined with the identified paediatric needs show, that the requirements and conditions for PUMAs need to be adapted to encourage more marketing authorisation holders to invest in voluntary paediatric development and encourage also national health systems to support such development by granting a return of investment.

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 the IKAM, there is a competition between the extension of existing treatments for paediatric use and the development of new therapies. For both it needs the data from clinical trials but the number of patients available, and much more important, willing to participate in trials is limited.

Data from new marketing authorisations in Europe prove that the number of new drugs available also for children increased since the enforcement of the EUPR. The replacement of existing therapies by new ones is a normal development and therefore it is difficult to tell if the situation improved or not. What lacks is the improvement of existing therapies for paediatric use as those are often widespread, known by healthcare professionals from an economical viewpoint, cheaper.

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?

For the extension of an existing marketing authorisation:

The costs for the development of e.g. a liquid as pharmaceutical dose form differ, depending on the stability of the substance. Including stability studies, there is range between 350.000 and 500.000 € (average). This does not include corresponding BE/BA studies, to be conducted normally in EACH intended paediatric age group. Bridging approaches between age groups have been proposed in recent time but acceptance in decision committees and authorities is questionable. Proposals to use literature sources or other scientific data, like retro perspective epidemiologic studies, is normally rejected. These additional costs (estimation about 1,0 Million € per study) are very often the reason for the decision against paediatric drug development.

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?

See above.

It seems to work well for new developments according to the EUPR. For PUMA, the encouragement for the initiation of voluntary research seems not to work. Support by national health systems is necessary to establish the concept of return of investment. The 10 years data protection is granted by the authorities and also controlled by them. Nevertheless, this is only a fictional market exclusivity. Generic adult drugs exist and as long as national systems will not support the prescription of existing drugs with paediatric indications but instead stipulate the use of the less expensive alternative adult drug, but with comparable dose forms (large tablets instead of micro tablets), the promised market exclusivity does not exist.

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 information available.

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?

Some procedural aspects have improved but the support of national paediatric drug development is still an unsolved problem. It is a general problem that in some areas the European law is not able to advise member states to act and decide accordingly. A mutual agreement or a statement of intent from national governments could help to improve the situation also in such areas, which have been identified by the previous status reports as issues still to be resolved.

An overview of national activities and supporting measures is helpful but not purposeful.

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?

No information available.

2.9. Deferrals

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

There seems to be a lack of understanding in the necessary study population for some paediatric trials and the availability of patients in the different age groups. It seems manageable and affordable for large companies to conduct studies in many member states, if they have to because it is mandatory. But it needs more understanding for smaller companies that they cannot afford such an European expansion of the area only to reach the required number of participants.

2.10. Voluntary paediatric investigation plans

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

IKAM disagrees with the proposed approach. In the US every drug development is discussed and accompanied by the FDA at a very early stage. Before the company starts with the research and development of a drug, it was made clear before what is necessary to get the authorisation and allowance for market access. This allows for a very early calculation of efforts and costs to support early decision making.

In the EU, there is no possibility for any estimation before. Even if the PIP states the necessary research effort, the national systems always insists on additional data to be generated. Comparison to different national standard therapies, additional data according to national law or provement of additional therapeutic benefit for patients. Even if this all was evaluated before by European experts groups.

2.11. Biosimilars

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

No information available.

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?

See also comments before.

The idea to stipulate voluntary paediatric research for products, no longer protected by patents etc. by granting a type of market exclusivity was introduced in the regulation afterwards because the paediatric needs will not be covered in the short run by development of new drugs. Existing gaps should be filled by the extension of existing marketing authorisations. The approach on a European level was reasonable but unfortunately, the national systems with the intention to reduce drug expenses at all costs lead to a situation where the concept works against the forces of the market.

The PUMA concept was doomed, because the idea that the national systems cover the investments for voluntary paediatric drug development where designed to fail.

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?

There is no guarantee that conducting a study within a PIP finally leads to a new paediatric drug. Incalculable risks while the development or the appearance of new requirements for research may lead to a decision for a stop of the development. There is no mechanism in place to take over or continue such a development financed by other interest groups or government projects. For example in the US such mechanisms exist, making it possible to finalise a development program by other institutions.

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?

Additional costs will add to the reasons for negative decisions of companies for voluntary paediatric Development.

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?

The regulation created a broader discussion on paediatric research. Knowledge and experience increased since 2007. But it also has created a vast array of new conflicts of interest. Development costs for new drugs increased and hopefully, this did not caused decision against other drug development projects. We have no information about company projects not proceeded because of negative decisions triggered by total budget availability.

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?

Extrapolation of results and data across age groups as well as the use of computer assisted modelling and calculation of drug doses and effects might reduce the development costs. But this will only work if such approaches are accepted by regulators and responsible expert groups.

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?

It needs government supported education campaigns to confess parents allowing their children to participate in clinical trials. Such campaigns could be initiated in a joint approach with clinical trial sponsors, academic and industry. Also the public opinion created by negative articles and reporting in the lay press and the general media will result in loss of public trust in pediatric research. Government support could lead to a more positive opinion also in the media.