

# Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

## 1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

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**Please indicate whether you are replying as:**

- A citizen (German citizen) ✓
- A business (klausrose Consulting, Pediatric Drug Development & More, Aeussere Baselstrasse 308, 4125 Riehen, Switzerland) ✓
- 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: Father of a severely handicapped child (rare congenital syndrom)

**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?

- Not in principle. Pediatrics as a sub-specialty of medicine developed without specific legislation, as did sub-specialties such as pediatric intensive care, neonatology, or Pediatric oncology (PO). PO developed off-label by systematically testing adult chemotherapeutic compounds in children. Already the title of consultation item no. 1 is misleading. The EU Paediatric Regulation (EUPR) imposes additional *pediatric* measures on drugs that are developed for *adult* patients. That is not developing "more medicines for children".
- Other ways for evidence-based pediatric medicine are additional "opportunistic" PK/PD analyses in patients that are treated off-label [7-9]
- The Thalidomide catastrophe led to first US pharmaceutical legislation in 1962 (Kefauver-Harris Amendments). European countries followed with comparable legislation. This prevents quack/unsafe medicine to enter the market. In the 1960ies, everything in this area was new. Many clinical trials were performed in prison inmates. Children were regarded as a vulnerable that needed protection. Today, most agree that children should be protected *through* research, but the boundary into adulthood as a legal versus biological/medical boundary is often confused.
  - Children are not another species. There is no reason why an antibiotic should not work in a child or even a baby. This holds true for many more medicines. Clinical trials are not a self-purpose, but should answer meaningful questions. Thus, separate registration trials are not necessary in every single age group. Where an adult dose is required, such as in adolescents, separate trials make limited sense.
  - Since the 1990ies, science and methodology in pediatric clinical pharmacology and modelling & simulation have advanced. Dose calculation in adolescents is not even necessary, as their body is sufficiently mature for adult doses. Doses in school children can be predicted and need confirmation in small PK/PD trials. The group where most research is needed is very young children, but they often have very different diseases compared to adults, and thus need other drugs.
  - For adolescents with otherwise predominantly adult disease types, e.g. specific cancer types (carcinoma) or pediatric multiple sclerosis, initially participation in adult pivotal trials should be facilitated as well as off-label treatment with newly registered compounds
  - For true pediatric diseases, new ways to facilitate drug development need to be explored. They should be based on the forces of the market, not against them.
- The EUPR has a substantial impact on drug development worldwide: an additional regulatory layer asks for clinical studies and other measures that are often of limited or no medical value and specifically in rare diseases harm children. Also multiple 5-years placebo control arms in frequent diseases such as hay fever prevents adequate treatment and allows disease progression towards asthma [14]. Preventing children from efficient treatment either off-label or in a beneficence-driven clinical trial means doing harm to children.
- The EUPR indeed leads to more pediatric trials. But do they make sense? Many compounds in PO are not licensed in children, but they save lives. It depends of the circumstances how labels

directly influence clinical decision making. In PO, the treating physicians know what they are doing. Children need neither "more" medicines nor "more" clinical trials, but medicines whose use in children is based on sufficient knowledge by the treating doctor or pharmacist. Such knowledge does not simply come out of labels. Transfer of medical knowledge is based on medical/ pharmaceutical university training, followed by bedside training. It is complex. The regulatory authorities (RAs) and the labels they approve play a key part in this, but the RAs are not clinical decision makers.

## 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 population" is defined in article 2(1) EUPR as everybody between birth and 18 years. The learnings that led to first US pediatric legislation in 1997 were those of pediatric clinical pharmacology (PCP) *in babies and infants*, not in legally minors of all ages.
- EMA and the European Commission constantly mingle two different issues: label change(s) and availability. Once a drug is licensed in adults, it is available. It may not have (yet) a label in minors, but physicians can prescribe it. Off-label used is addressed e.g. by statements from the American Academy of Pediatrics [5]. There is no corresponding statement on EU level.
- New treatment options evolved during the last decade, e.g. ivacaftor for roughly 5% of patients with cystic fibrosis (CF). But this occurred *despite* the EUPR, which only added numerous PIP modifications without substantial positive contribution [15]. There are no important new treatment options made available *through* the EUPL. The examples listed in the EMA 10-year-report [4, page 14] list of adult medications where the PIPs have enforced creation of additional pediatric data. As far as the patients were adolescents, these data are useless; the maturity of their body allows the same dose as in adults. Clinicians around the world treat patients off-label with newly available drug. Instead of enforcing extremely costly regulatory trials, it would make more sense to create the needed data in an "opportunistic" way in the framework of therapeutic off-label use combined with PK/PD sampling AND collaborating with the FDA [7-9].
- As long as children are very young, their absorption, distribution, metabolism and excretion (ADME) differ from adults, resulting in danger of under- or overdosing. But not in adolescents whose body becomes adult before the 18<sup>th</sup> birthday. Babies and infants have the highest medical needs, but the PDCO's activities are more focused on other age groups [4]
- Differentiation is needed also in clinical terms. There are e.g. cancer types that are relatively frequent in adults, but can affect rarely or very rarely also children, e.g. melanoma or non-small-cell lung cancer (NSCLC). But these "adult" cancer types (solid tumors in adults are mostly carcinomata) do not occur uniformly across all age groups. Instead, they are rare in adolescents and extremely rare in young children. PIPs insist on separate safety & efficacy and/or pharmacokinetics/ pharmacodynamics (PK/PD) trials sometimes in adolescents, sometimes in the "paediatric population" as defined by the EUPR. This does not make medical sense. Instead, companies need to be encouraged to open recruitment to the very few adolescents carcinoma patients into adult trials. For the extremely rare cases in younger children, separate registration trials are not feasible. There, the "opportunistic" study approach [7-9] should be used: Whenever specialized centers decide to treat off-label, they can take additional blood samples for PK/PD measuring. Such an approach, done only in one or a handful of children, can help other medical doctors globally. Such a collaboration exists between the FDA and specialized clinical centers,

but is at present not possible in the EU. The EMA's fundamentalist approach is focused on regulatory trials, even if they are not feasible. Two PIP-triggered clinical trials in adolescents with metastasized melanoma had to be terminated in 2016 [2,10]; in the verumafenib trial, 5 of 6 patients, median age 15.8 years, died [2,12].

- The EMA claims that the first recombinant asparaginase has been made available for the treatment of pediatric acute lymphoblastic leukaemia (ALL) [4, page 14]. The survival rate of pediatric ALL is already around 90%. For pediatric ALL, a new form of asparaginase is a very minor factor needed to improve treatment. What children with ALL really need is innovative treatment that is less toxic than classic chemotherapy.

### 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?

- We know from the EMA statistics that the number of pediatric indications as per label has increased. Does this result in better treatment of children? Not in specialized areas such as PO, neonatology, or pediatric intensive care. It might change prescription patterns in more marginal areas, e.g. prescriptions by GPs.
- EMA and the European Commission constantly mingle two different issues: label change(s) and availability. Once a drug is licensed in adults, it is available. It may not have (yet) a label in minors, but physicians can prescribe it. Off-label used is addressed e.g. by statements from the American Academy of Pediatrics [5]. There is no corresponding statement on EU level.
- The EUPR has also prevented pediatric medications to be introduced into the EU. The PIP request on glycopyrronium was rejected by the PDCO [3]. Glycopyrronium is FDA-licensed since several years [5]. Thus, medications for children blocked from registration by EMA/PDCO should be balanced against new pediatric labels.

### 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 estimated annual costs incurred by industry of € 2.1 billion only reflect costs for executed clinical studies and other PIP measures. The European commission (EUC) argues that if compounds are discontinued, this would even reduce the PIP costs. But the overall EUC's assumption is that the PIP-demanded studies make medical sense. This is, however, not the case in many PIP-demanded studies, specifically in PIPs that regard diseases rare in children, such as melanoma (12, 16-21), pediatric multiple sclerosis (13), and in studies that requested safety & efficacy clinical trials in adolescents. Consultation item 2.4 disregards:

1. The annual costs are expenses for studies of whom a relevant portion is questionable.

2. Drug development is not a mechanical, but involves inventions, creativity, and more. The EUPR is *discouraging* companies from developing medicines for children. This damage is difficult to assess, but is certainly of a higher dimension than the annual € 2.1 billion
3. The EUC's calculation omits the risks companies run by executing EMA/PDCO-demanded questionable and unethical clinical trials. Two such trials had to be terminated in 2016 [2,10]. In the Vemurafenib trial, of 6 recruited patients 5 died. These patients with a median age of 15.8 years received a first dose below the FDA-approved therapeutic dose of vemurafenib. They should have been treated with at least the FDA-approved therapeutic dose, probably better with a combination of biologics FDA-approved for metastasized melanoma to prevent development of resistance in the malignant melanoma cells as long as possible [12]. Once parents will realize that many PIP-demanded clinical trials are unethical, they will sue for damage. They will sue institutional review boards (IRBs)/ ethics committees (ECs) that should never have accepted these trials, they will sue the companies that initiated these trials, and clinical research organisations (CRO) that are/ were involved. The US legal system allows for punitive damages. These can be as high as dozens of billion Euros, which can result in the bankruptcy of a company. Companies that comply with EMA-demands without building up from the start iron-clad legal cases to prove that they were coerced into these trials should already now build up reserves for damage lawsuits that will come in in the near to middle future.

## 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?

- Some procedural aspects have improved, such as splitting PIPs if the compound can treat very different diseases.
- However, on the content level the EUPR's implementation is getting worse. The melanoma PIPs do more harm than good [12, 16-19]. The melanoma class waiver was revoked in 2008. In 2015, the EMA issued a new decision on class waivers, making PIPs obligatory for drugs targeting diseases that are extremely rare in children, such as liver cancer or amyotrophic lateral sclerosis. The same concerns apply as for those already discussed in the literature, including leukemia, melanoma, and multiple sclerosis (MS) [11-13, 15-21].

## 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?

- See comments on consultation items 2, 4, and 7

## 2.9. Deferrals

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

- PIPs for allergen products for specific immunotherapy (SIT) demand clinical trials that, if performed, will include ten thousands of children & adolescents with hay fever into 5-years double-blind placebo-controlled medically worthless trials until 2031 [14].
- Deferrals should be given in cases where new compounds have the potential to harm children, e.g. cytotoxic compounds. PIPs have triggered pediatric trials in compounds whose development was later terminated [16].

## 2.10. Voluntary paediatric investigation plans

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

- The author does not see any reason why companies would seek a voluntary PIP.

## 2.11. Biosimilars

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

## 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 PIP concept has not resulted in disappointment, but was a failure. Recital 2 of the EU Pediatric Regulation clearly states that the legislation is intended to work against the forces of the market. Thus, they were 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?

The EU Paediatric Regulation has created a vast array of new conflicts of interest:

- Commercial clinical research organisations have a commercial interest in clinical trials with children, irrespective if the trials make sense or not.
- The EMA is forcing companies to perform questionable clinical trials. The justification of revoking the melanoma class waiver in 2008 was not based on science. PDCO members and EMA employees might lose their job once it comes out that many PIP-triggered trials are useless and/or even harm children. This is a conflict of interest: they might defend EMA positions, even if they know that they are wrong.
- Pediatric clinicians in academia are often short of research funds. They work with the EMA in the European network of pediatric research coordinated by the EMA. Also this is a conflict of interests. *One* pediatric melanoma trial might at first glance appear to be scientifically sound.
- The many PIP-demanded melanoma trials, including those first initiated and later terminated [2,10], those ongoing [12], and those that will start eventually [12] are unfeasible, questionable and unethical. Clinicians and IRBs/ECs should check [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu) for other trials competing for the same potential study participants.
- There were 26 clinical centers in the US, EU and Australia that participated in the terminated verumafenib trial [2], and 30 centers in the US, EU and Mexico in the terminated ipilimumab clinical trial in adolescents with metastasized melanoma [10] Thus, more than 50 IRBs/ECs will have to justify why they didn't reject the two trials that later had to be terminated. Warnings against such trials were published since 2014 [17-19]

## 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?

- Even without fees the PIP system is not only damaging pediatric research, but it represents a danger for the public trust in pediatric clinical research.
- Bureaucracies have the tendency to expand until they are stopped. Regarding the PIP system, it is logical for EMA/PDCO that they would like to expand their activities, as can be seen by the class waiver decision from 2015. This will make the negative consequences of the PIP system even worse. In short term, it might allow more employees to be hired by EMA/PDCO.
- In conclusion, a fee system would make the negative consequences of the EUPR even worse.

## 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?

- See consultation item no. 13

## 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?

- For diseases relatively frequent in adults and rare in children, the demanding regulatory pediatric clinical trials for every single new compound that is developed for adults is not working. This was shown as early in 2007 [1] and newly from 2014 on [11-21]. A new concept is "opportunistic" pediatric studies, i.e. taking samples when a given compound is given to a patient with therapeutic intentions [7-9, 12], thus allowing PK/PD assessments without large regulatory unfeasible clinical trials.
- The FDA has moved to more extrapolation in antiepileptic compounds
- Modelling & simulation have reduced the need to run separate efficacy studies in the various pediatric age groups.

**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 author's personal way to investigate the EUPR more in depth came from an initial positive position. The author has vast hands-on experience in negotiating pediatric development concepts first with the FDA and then with the EMA. It took several years to build up a systematic critical position, first published in 2014 [19]. From there followed further investigations of different clinical areas [11,13-16] and finally of the wording of the EU Pediatric Regulation, specifically the first 3 recitals and the definition of the "paediatric population" in article 2(1) [12]. The implementation of the EUPR reflects its wording. In the hands of a more pragmatic administration such as the FDA, its implementation might have been less exaggerated.
- Over the coming years more challenges rooted in the flaws of the EUPR and its implementation by EMA/PDCO will emerge. Pharmaceutical companies must now protect children against EMA/PDCO. Institutional review boards (IRBs)/ ethics committees (ECs) will have to learn fast. They should reject questionable studies that are based on PIPs. They should screen for all pediatric studies submitted for approval if comparable trials are listed on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu). They also should suspend ongoing questionable pediatric studies.
- Angry parents will sue anybody involved in questionable pediatric studies, including medical doctors, IRBs/ECs, hospitals, pharmaceutical companies, and more.
- Parents will no longer allow their children to participate in clinical trials.
- When this discussion reaches the lay press and the general media, it will result in loss of public trust in pediatric research. People will ask why nobody noted these challenges earlier.
- Angry parents will sue anybody involved in questionable studies, including medical doctors, IRBs/ECs, pharmaceutical companies, clinical research organisations, and more. The EUPR will thus contribute to a general loss of credibility of the medical and academic system in the western world.



## **Abbreviations**

ADME	Absorption, Distribution, Metabolism, Excretion
EC	Ethics Committee
EUPR	EU Pediatric Regulation
IRB	Institution Review Board
PCP	Pediatric Clinical Pharmacology
PDCO	Pediatric Committee
PO	Pediatric Oncology

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