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 Society of Pediatrics and Adolescent Medicine

Transparency Register ID number (for organisations):

Country: Germany

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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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Please indicate whether you are replying as:

- o A citizen
- o A business
- X A non-governmental organisation (NGO)
- o An industry association
- o A patient group
- o A healthcare professional organisation
- o A cademia or a research or educational institute
- o 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

- o 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?
It is agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines. However, if we really wish to reduce the use with off-patent medicines in the paediatric population, additional structural improvement or changes in the infrastructure of the health system and clinical research are needed (see below). Furthermore, the current regulation does not meet the very specific needs of the intra- and extra uterine fetus.

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?
Respectable progress has been made since the Paediatric Regulation was adopted in 2007. It represents a great success to enable companies to screen drugs that have been developed for adults for their potential use in children. However, a much broader approach is required to support development of drugs that meet specific pediatric needs. Many pediatric diseases occur primarily in during childhood and are very specific for this population and need a very specific therapeutic approach. This is especially true for the intra- and extra-uterine fetus. In consequence, an entire pipeline for drug development is required exclusively for that population. Especially in these cases, pharmaceutical companies cannot benefit from co-using the drug in adult population. As a consequence, legislation should not only focus on screening drugs for adults for their potential use in children. More importantly, legislation should encourage development of drugs that focus on the very specific needs of infants and children, which are unlikely to have a good pay-off for companies.

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?
Not only pure inertia (in the system) are the problem for not switching to newly authorised medicines, especially if it comes to the “long-established-products”. Learning to appreciate these new paediatric medicines, the prescribing paediatrician needs

to be more familiar and trained in paediatric pharmacotherapy as presently. Moreover, also the national medical service of the health insurances has to be trained in a way, that it will reimburse/cover the higher prices for the newly authorized paediatric medicines even if there are cheaper products for off-label use on the market. In summary, the number of new paediatric medicines available in Member States has not substantially increased.

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?

Even if a company decides to discontinue an adult development programme for any reason, this does not justify to discontinue automatically the paediatric programme, especially ife there is no such reason in the paediatric population and as long as there is a substantial unmet medical need. In that case it is necessary to extend the competence of the EMA/PDCO and enable the agency to prevent companies from pursuing this merely profit driven practice.

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?

Currently the rewards induced by the paediatric regulation are apparently not sufficient or not attractive enough to induce a broad active involvement of the pharmaceutical industry towards the development of better and safer drugs for the paediatric population

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 comments

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?

Since it implementation 10 years ago the regulation has facilitated the development of PIPs probably indicating an increasing awareness of pharmaceutical R&D for the specific needs of the paediatric population. However, despite this partial progress so far the regulation as not reached its goal to reduce off-label medication in the paediatric population. While an increased number of Paediatric Investigational Plans have been filed over the past years the absolute number of drugs that have been specifically investigated and licensed for the paediatric population did not increase.

***In addition "in principle the regulation should also lead to more (cost-)efficient R&D, as it makes it possible** to consider integrating adolescents into adult trials thereby reducing overall study costs."*

Adolescence represents a very unique vulnerable and challenging stage of human development, which is characterized by a period of final growth, reproductive maturation, and cerebral remodelling (Seyberth & Kauffman, 2011). Moreover, depending on the state of puberty, patients between the age of 12 to 17 years are quite heterogeneous. In consequence it is not justified to assume that adolescents represent a population biologically similar to adults.

There are only certain exemptions, such as seen in the EMA/PDCO Standard Paediatric Investigation for Allergen Products for Specific Immunotherapy using the concept of extrapolation, modeling and simulation with the intention to reduce of the number of study subjects. We should always be aware that we neither have disclosed all unforeseen changes during maturation nor do we have the appropriate parameters or biomarkers (for these developmental changes) that need to be considered for modelling and simulation. Thus, there are certainly some limitations for this concept. Having said all this, it is difficult to understand that the impact of acceptability of extrapolation on sample size planning was 100% in anaesthesiology (see Fig.13 on p. 50 of the 10-Year Report). It has always been my experience that the younger the child the more difficile is general anaesthesia.

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?

Before coming to any final decision on granting an exemption (a waiver), one should be familiar not only with the medicine's mechanism of action but also with the (molecular) physiology and pathophysiology at the different stages of development in the paediatric population ranging from the newborn infant, the toddler, the child, and finally through the adolescent.

One wonders how the Paediatric Committee (PDCO) would have decided today on the COX-2 selective inhibitor celecoxib (a NSAID with less gastrointestinal adverse drug reaction) that is primarily indicated for the treatment of patients with osteoarthritis, a degenerative disease of the joints. There might also be an indication of this drug to treat preterm infants with either symptomatic patent ductus arteriosus or life threatening renal salt and water wasting (antenatal Bartter syndrome). In both (neonatal) diseases increased prostaglandin synthesis is involved in the pathophysiology as it is in osteoarthritis of the elderly.

From the pure regulatory aspect, the present waiver concept seems to be quite straightforward. However, in some cases this concept might be too simple and does not fulfill the intention to develop innovative medicines for children.

2.9. Deferrals

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

In principle, a deferral for finalizing the paediatric development appears to be essential to avoid any delay in the initial marketing authorisation application for other population, essentially for adults. This is accepted taking into account that the development of a

medicinal product for paediatrics is more challenging and presumably take much longer. However, the PDCO has granted a deferral in almost every PIP agreed so far, even in those cases where children are seriously suffering as authorised medicines are (not yet) available (e.g. infectious disease like treatment of HCV infection, paediatric oncology).The EMA/ PDCO/ EC needs to revisit the eligibility for applying a deferral to the PIP. The current practice of granting deferrals very generously has many negative implications regarding the needs of the pediatric populations. It appears that many important developments for the pediatric population are delayed due to this practice.

2.10. Voluntary paediatric investigation plans

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

The EC may consider the advantages of the "written request" of the US legislation. It is repeatedly seen that companies are ignoring urgent paediatric (therapeutic) needs and referring to the constitution that guarantees the right to refuse any business without sufficient return on investment. Therefore, a strong incentive should apply for any successful voluntary PIP.

2.11. Biosimilars

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

In this case the obligation to transfer the marketing authorisation to another company is (fully) justified, but should include the authorised paediatric indication. Otherwise, if the company is not cooperative and withholds the marketing authorisation, the agency may consider publish this inappropriate and un-ethical behavior.

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?

A significant number of drugs is indispensable for pediatric therapy and has to be used off-label while they are only authorized in adults but not in children. In many cases, health insurance companies use this situation to deny reimbursement of treatment with these drugs in the paediatric population. This clearly poses an extreme disadvantage for infants and children: the refusal of the health insurance system to pay for drugs (especially if they are expensive) in off-label use leads to the withholding of effective treatment from children and therefore clearly represents a disadvantage.
Still, the PUMA concept represents – at least to some extend – an incentive to carry out research focused on the specific needs for pediatric population. On the other hand the use of off-label drugs with the similar ingredient at lower-cost represents a problem that is faced by many physicians. Restrictions in health-care expenditures are required and thus, it is always difficult to decide between an in-expensive off-label product or an expensive authorized product. Nevertheless, we consider the approach of PUMA as feasible and support the continuation of the concept. We would also like to make aware of the Newborn

Drug Development.
Therefore, the EMA should search together with the pharmaceutical industry for more attractive incentives or awards. It should be kept in mind that the bulk of paediatrics medicines, that are used off-label, are off-patent.
In addition, EMA and the national agencies should highlight and educate the national health officials about this problem/issue that cannot just be solved by the EMA. It is unacceptable when on side health insurance companies refuse to pay for very promising medicines that still have no paediatric marketing authorization and on the other hand health insurances demand from physicians the prescription of the cheaper but not adequately labelled products despite when at the same time the correctly labelled but more expensive products are on the market.

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 issue of performing clinical trial in pediatric population poses a very specific problem. Whereas appropriate ethical research is of outmost importance, there is a potential risk of delaying (or even preventing) the introduction of a beneficial product into the clinical routine for several reasons: some trials are competing among similar populations making recruitment difficult; some interventions (during emergencies) have to be given very early, making the consent process with the parents very difficult and posing additional (psychological) harm to the parents; some drugs that are blockbusters in adults are “investigated” in children, without any significant hope of beneficial effects in that population. Conversely, drugs that turn out to not be efficient in adults, but may prove beneficial in children, infants and newborns are not being pursued because of lower return on investment for the pharmaceutical company compared to adult indication. This is unacceptable.
Certainly, the PDCO should try to prevent that multiple companies carry out uncoordinated activities in children in parallel for the same adult disease; especially, when there is no urgent paediatric need (e.g. type II diabetes). If they are not willing to collaborate with each other, the benefits/rewards of the Paediatric Regulation should be granted (if possible) only to one company. Any innovative approaches of the PDCO to priorities, which medicine should be developed in children, as outlined in the 10-year Report, are certainly appreciated.

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?

The current system of giving the advice for pediatric drugs free-of-charge is strongly supported. On the other hand we are aware of the potential problem of not reimbursing national experts in the field. The waiver for fees by EMA is somewhat unrealistic, especially when one takes in account that the companies’ compensation to their advisers and experts is quite respectable. Thus, there is good reason to believe that on the long run the recruitment of highly qualified people will be quite difficult for the EMA/PDCO. Consequently, these upcoming difficulties will require changes in the approach
There are possible solutions:

A contract could encourage companies which subsequently established a drug successfully in the market to pay the fee in retrospect.
Secondly, the scientific advisers could be "reimbursed" by other means, such as a system of credit points that enables them for EU-funding (if two proposals are scored equally, the "credit points" will help to decide).
Another solution could be that companies, which have not accurately fulfilled their obligations/requirements from the PIP, will be charged for all services that already had been provided to them by EMA/PDCO.

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 effects of the Paediatric Regulation on paediatric research are quite impressive as far as it concern the process of product development and its associated regulatory affairs. It has primarily not been intended to increase our basic understanding and knowledge of (all) maturation processes and the (patho-) physiology of diseases at the quite different stages of development of the paediatric population. However, we should be more aware that there are still quite some gaps in this understanding and knowledge. Therefore, besides the implementation of the Regulation, academic teaching and training should have a stronger focus on maturation processes and paediatric physiology. In addition, IMI public-private partnership, an innovative medicines initiative, could be one way to find funding for clinical research infrastructure from public and private sources.
Whereas networks are a prerequisite for sound research in the field of pediatrics, it is not the most important aspect. In our opinion, strong local networks are good; however, the development of a "network of networks" provides no further advantage. In most cases, the players in different networks are the same individuals.

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?

The current concept of pediatric-specific legislation is mainly focused on "traditional" drug development. Currently new strategies are emerging and require new approaches. Beside the concepts of "adaptive pathways" and "precision medicine" it is of importance to pave the road for "cellular therapies" which currently offer a great potential. On one hand is of importance to protect infants and children from potential harm associated with these therapies, on the other side, legislation should be better adapted to meet the specific demands associated with that concept. Currently, it is rather difficult to bring a cellular product from bench to routine bed-side usage, due to difficulties in legislation.
It is quite reasonable to believe that precision medicine, which is based on patients' individual genetic composition, will be (potentially) more important in paediatric pharmacotherapy in the future, particularly in paediatric oncology. However, for the time being and also in the near future the dynamics of maturation remain to be the most dominant factor. Thus, the younger the patients the more influential on personalised pharmacotherapy are the developmental and not so much the genetic aspects.

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?

In general the expectation of this piece of legislation or better of the global initiative of "Better Medicines for Children" is or at least was to facilitate an overall safer and more innovative drug treatment for children. Achieving this objective involves, on the one hand, taking full advantage from the know-how and the infrastructure that has been developed during the implementation of the Paediatric Regulation and on the other hand, all the potential arising from the expansion and knowledge of modern medical sciences and methodology that enables us to conduct studies in vulnerable patient populations that had not been impossible and/or unethical in the past.

However, at the same time health care systems throughout Europe have undergone dramatic structural changes following an ever increasing economic pressure. This development strongly influences working conditions of the medical staff in general. Moreover, an enormous burden of bureaucracy and regulation has markedly grown in clinical research, which unfortunately also does affect the essential pilot and Proof-of-Concept studies. Furthermore, rarely young physicians have had a sound preclinical training in basic science, such as in (molecular) physiology/pharmacology or biochemistry that enables them to develop their one clinical research projects. This ability also might include the skills to detect and identify still existing gaps in our current knowledge about old, off-patent medicines. With this qualification they should also be able to provide the basics for extrapolation and simulation as well as to develop the essential biomarkers and endpoints to conduct paediatric studies.

In consequence, this comprehensive qualification needs to be fostered by training the next generation of paediatricians. However, unfortunately the young colleagues often have just passed some GCP-courses or at the best training course on the paediatric regulation that qualify them to be a useful "medical technician" for pharmaceutical companies on the ward or in the clinics. Hopefully, the GRiP Network of Excellence with its master program in paediatric clinical pharmacology will provide a deeper knowledge in the basics and dynamics of paediatric pharmacology (on an international level). However, also here we need highly qualified academic lectures and teachers with clinical expertise. They will probably not come from Industry.

Why not getting started on an ambitious MD-PhD-programme right now or as soon as possible, preferable with the focus on paediatric pharmacology, to generate a sufficient number of independently thinking and working physician scientists, who later should have a chance to enter in an academic tenure track programme in clinical research institutions or academic hospitals?

Furthermore, we would like to focus on the very specific needs not only of the newly born infant but also on the not yet born infant, eg. the intra-uterine fetus. Both groups represent the most vulnerable patients with very specific needs. When compared with adult (and to some extend in pediatric) patients, the intra- and extra-uterine fetus (preterm infant) do have the following characteristics that make drug development very unique for this population:

- the pharmacodynamic is affected by immaturity of many organ systems
- the body composition and thus distribution of drugs is very different.
- dosage of drugs is much lower and thus, drug development is less lucrative for companies

In summary, there is a huge need to consider these aspects in drug development for that

specific population. We therefore welcome the efforts of the European Union to have specific pediatric legislation to support introduction of drugs for pediatric population, however we would really encourage the European Commission to specifically consider the population of intra- and extra-uterine fetus. Furthermore, we would encourage focusing on the development of cell-based therapies. In our opinion, the current legislation does not consider the very specific needs to develop cell-based therapies in neonatal or pediatric population