Response of the

German Medical Association (Bundesärztekammer)

Consultation in relation to the Report on the Paediatric Regulation

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Preliminary remarks

The following observations respond to the European Commission´s targeted stakeholder consultation on the experience acquired with the Paediatric Regulation (EC) No.1901/2006[1], carried out from 15 November 2016 until 20 February 2017. They are based on expert input received from the Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft). Our answers relate to the questions contained in the consultation document[2] and should be read in conjunction with these.

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: Drug Commission of the German Medical Association

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Please indicate whether you are replying as:

- X A healthcare professional organisation

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

[1] ec.europa.eu/health/human-use/paediatric-medicines/developments/2016_pc_report_2017_de
[2] ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/paediatric_consultation_document.pdf

2. PART II – 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?

The Paediatric Regulation has definitely stimulated drug development for children in Europe, but has done so only with partial success and in a specific way. Significant benefit was achieved for treating children with conditions, diseases or symptoms that resemble or are similar to those in adults (e.g. infectious diseases like HIV, autoinflammatory conditions like rheumatic diseases or multiple sclerosis, arterial hypertension). Thus, drug development for children was mainly restricted to underlying pathophysiological mechanisms well known in adults and transferable to children and adolescents.

Deficits in paediatric drug development are still present for conditions and diseases in neonates and children with a different pathophysiology from that of adults. For drug development in these cases a new approach or external support is necessary.

Specific legislation supporting the development of paediatric drugs is necessary to guarantee an evidence-based approach.
However, if we really wish to reduce the use of off-patent medicines in the paediatric population, additional structural improvements or changes in the infrastructure of the health system and clinical research are needed (see below).

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?

We agree that advances for new drugs in therapeutic areas and conditions for adults will translate into advances for children as well through the Paediatric Regulation approach. However, children in Europe do not benefit from new drug development in therapeutic areas that are not relevant to adults, since the starting point for most paediatric investigation plans is a research & development programme for adults. As a result, many unique health problems and diseases of the paediatric population are not (a priori) considered. This applies especially to younger children, such as the pre-term and term newborn infants.

Clear benefits have been achieved with regards to infectious diseases, allergies and autoimmune disorders. This is also partly the case for antiepileptic agents and antihypertensive agents, but only with new drugs (ACE inhibitors and Angiotensin II receptor blockers).

The 10-Year Report of the European Commission cites WHO data stating that the disease burden in the paediatric population based on DALYs in the EU is highest for mental and behavioural disorders (20% total DALYs). However, the Report states that “the need for medicines is not that high in this area” due to non-pharmacological treatment options. On the contrary, from an expert’s point of view, medicines for mental disorders in the paediatric population are needed and frequently administered - often in addition to non-pharmacological treatments. Many of these medicines are off-label. In order to address this unmet need, further funding is needed for research on off-patent medicines for paediatric use in mental disorders (e.g. age-specific data on pharmacokinetics, effectiveness, tolerability) in addition to the development of new medicines (see also comment on Item No 12).

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?
Paediatric Regulation has stimulated the awareness that there is also an urgent need to develop new treatment options for children by investigating dose finding, efficacy and safety of pharmaceutical agents used in children. With only two new approvals, the Regulation did not contribute to the availability of new treatment options in the area of mental and behavioural disorders, although for many treatment areas mentioned under 2.2, a clear benefit has been achieved and the number of new paediatric medicines available in Member States has substantially increased. However, not all physicians restrict their prescription to new licensed paediatric indications. Some also prescribe new drugs licensed for adults for off-label use in children and adolescents. The reason for this is a lack of knowledge and awareness of newly licensed drugs for children. To learn to appreciate these new paediatric medicines, the prescribing paediatrician needs to be more familiar with and trained in paediatric pharmacotherapy.

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?
If a company decides to discontinue its adult development programme for any reason, this does not justify automatically discontinuing its paediatric programme as well. There is no cause for this and there is a substantial unmet medical need. In such a case, it is necessary to extend the competence of the EMA/PDCO that enables 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?
The reward system appeared to be sufficient for drugs commonly prescribed in adults. If companies start the studies proposed by the paediatric investigation plan early and there is a clear regulation that treatment of children and adolescents with new drugs is primarily restricted to the protocol and prohibiting the study and publishing of off-label case series, the children in the Member States would benefit earlier. In this context, companies should not be able to support early off-label use.

2.6. The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?
It is agreed that the orphan reward has limited impact. Also the blockbuster aspect is well received.

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?

It is agreed that the implementation has improved over time and some of the initial problems have been resolved. Nevertheless, limitations will remain with regard to the lack of stimulating high-quality research for paediatric medication in paediatric diseases not relevant to adults, as well as the lack of incentive for licensing drugs with expired patent protection (PUMA regulation).
Common commentaries and common study protocols (for EMA and FDA application) appear to be helpful.
The following proposal should be critically scrutinized:
"In principle it 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 is a very unique, vulnerable and challenging stage of 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 ages of 12 and 17 years are quite heterogeneous. That is why we cannot (uncritically) lump together these patients with (post-pubertal individuals and) adults. There are only certain exemptions, as is seen, for example, in the EMA/PDCO Standard Paediatric Investigation for Allergen Products for Specific Immunotherapy.
When using the concept of extrapolation, modelling and simulation with the intention of reducing the number of study subjects, we should always be aware that we have neither 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. As a result, this concept certainly has some limitations. 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 the experience that the younger the child, the more difficult general anaesthesia is.

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?

It is agreed that class waivers based on diseases in adults are counterproductive for some topics, e.g. paediatric oncology. In the past, several opportunities were missed for developing new treatment options, e.g. for solid tumours.
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 to 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 pre-term 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 is the case in osteoarthritis of the elderly.

2.9. Deferrals

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

It is agreed that the deferrals have not delayed drug development and accessibility for new drugs in adults. It is also useful to wait with studies in children until basic adult experience has been concluded with regard to positive efficacy, tolerability and lack of serious toxicity.
However, if a new efficient drug for adults is available, the delay in paediatric study protocols

definitely induces off-label use in children. That has been the case for new immunosuppressive agents in organ transplantation. Paediatric patients were treated off-label for assumed urgent need and with a misguided approach to help the children with off-label treatment. These off-label treated patients were not available for clinical studies and patient recruitment was delayed, became more difficult and was ultimately impossible.
Thus it is not uncommon for paediatricians to use this off-label approach because paediatric study protocols with early first-in-child studies (evidenced-based dose finding and tolerability) come too late. It should be considered whether a regulation should be instituted that first-in-child use may only be performed in a well-planned and executed study in which all eligible child patients can contribute to finding the right dose, tolerability and efficacy in an evidence-based way.
Thus, early monocentric case series become unethical.

2.10. Voluntary paediatric investigation plans

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

A programme to stimulate and promote paediatric-only development for paediatric medicines is of major interest for certain paediatric diseases. This programme would be able to provide an alternative approach for high quality drug development, particularly for children.
The “written request” modality of the US legislation is also a good example. It is not uncommon for companies to ignore urgent paediatric (therapeutic) needs and to refer to the constitution, which guarantees the right to refuse any business without sufficient return on investment.

2.11. Biosimilars

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

Children should also benefit from biosimilars. Therefore there is no alternative but to investigate biosimilars in children to an adequate extent.

In this case, the obligation to transfer the marketing authorisation to another company is (fully) justified. Otherwise, if the company is not cooperative and withholds the marketing authorisation, the agency may consider making this inappropriate and unethical behaviour public.

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 programme as intended in the Paediatric Regulation was highly disappointing with regard to overcoming off-label use. This is partially due to the fact that new paediatric formulations will not be prescribed by general practitioners and paediatricians because off-label prescription is still possible and common. The prescribers do not recognise the benefit clinical studies will add for finding the right dose and a formulation suitable for children. Additional funding, e.g. for pharmacokinetic research in different age groups for finding the right dose, will help those children who are in need of the drugs.
Nevertheless, the main goal of PUMA remains absolutely worth aspiring to. 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 paediatric 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, which cannot be solved by the EMA alone. It is unacceptable when, on the one hand, health insurances refuse, for financial reasons, to pay for very promising medicines that still have no paediatric marketing authorisation and, on the other hand, demand that physicians prescribe cheaper, but not adequately labelled products, despite the fact that the correctly labelled

but more expensive products are simultaneously on the market.
However, it could be counterproductive if pharmaceutical companies have gone into the market with excessively high prices in mind(e.g. inhaled nitric oxide (iNO) for persistent pulmonary hypertension of the newborn (PPHN) or propranolol for infantile haemangioma).
Funding from public sources for research on off-patent medicines should be maintained. Since parents are often hesitant to agree to the participation of their children in paediatric studies, especially concerning medicines for mental disorders (see also comment on Item No 2), information and education of the public on the necessity of clinical studies is needed.

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?

With respect to the development of new drugs for children, early paediatric clinical studies are urgently needed to prevent unregulated and extensive off-label use. Therefore new drugs should be allowed early and initially only in high quality research protocols.
The PDCO should try to prevent multiple companies from carrying out activities in children parallel to doing so 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) to only one company. Any innovative approaches of the PDCO to prioritise which medicines 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 efforts and costs of paediatric drug development should be borne by the EU for the children. This is a good investment for the children of Europe.
The major reason why the PDCO procedures are not financially compensated is presumably that the paediatric investigation plan process is currently exempt from the fee system. This offer by the EMA is somewhat unrealistic, especially when one takes into account that the companies' compensation to their advisers and experts is quite respectable. Thus, there is good reason to believe that in the long run, the recruitment of highly qualified people will be quite difficult for the EMA/PDCO. Consequently, these upcoming difficulties will require a different approach.
As a very first step, it is recommended that companies which have not accurately fulfilled their obligations/requirements be charged for all services that had already 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 concerns 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, in addition to the implementation of the Regulation, academic teaching and training should have a stronger focus on maturation processes and paediatric physiology. One must hope that the IMI public-private partnership, an innovative

medicines initiative, will be one way to find funding for clinical research infrastructure from public and private sources.

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?

Children have the right to benefit as adults from new concepts and new research projects.
It is quite reasonable to believe that precision medicine, which is based on patients' individual genes, will (potentially) be more important in paediatric pharmacotherapy in the future, particularly in paediatric oncology. However, for the time being, and also in the foreseeable future, the dynamics of maturation continue to be the most dominant factor. Thus, the younger the patient, the more personalised pharmacotherapy is influenced by developmental, rather than 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?

The Regulation's implementation only partly fulfilled expectations, but further effort is necessary to study new drugs in children in all age groups earlier and more consequently.

The expectation of this piece of legislation, or rather of the global initiative "Better Medicines for Children", is or at least was that sooner or later we will come up with an overall safer and more innovative drug treatment for children. Achieving this objective involves, on the one hand, taking full advantage of 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, which had been impossible and/or unethical in the past.
At the same time, however, as economic pressure on medical staff has significantly increased, an enormous burden of bureaucracy and regulation has markedly grown in clinical research, which unfortunately also has an impact on the essential pilot and Proof-of-Concept studies. Moreover, young physicians have rarely received sound preclinical training in basic science, such as in (molecular) physiology/pharmacology or biochemistry, to enable them to develop their own clinical research projects. This ability also might include skills for detecting and identifying existing gaps in our current knowledge of old, off-patent medicines. With this qualification they should also be able to provide the basics for extrapolation and simulation, as well as develop the essential biomarkers and endpoints to conduct paediatric studies.
Therefore, this comprehensive qualification needs to be fostered by training the next generation of paediatricians. However, these young colleagues have often just completed some GCP-courses or, at best, the training course on the Paediatric Regulation, which qualify them to be a useful "medical technician" for pharmaceutical companies on the ward or in the clinics. The GRiP Network of Excellence, with its masters program in paediatric clinical pharmacology, will hopefully provide a deeper knowledge of 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 get started now, or as soon as possible, on an ambitious MD-PhD programme, preferably with a focus on paediatric pharmacology, in order to generate a sufficient number of independently thinking and working physician scientists who could later have the option of entering an academic tenure track programme in clinical research institutions or academic hospitals?