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**BY E-MAIL**  
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European Commission  
Directorate General for Health and  
Consumers (SANCO)  
B-1049 BRUSSELS

**SUBJECT:Public Consultation: General reporting experience acquired as a result of the application of the Paediatric Regulation. experience acquired' and 'lessons learnt'**

Dear Madame/Sir,

PPTA is the international trade association and standards-setting organization for the world's major producers of plasma derived products and recombinant analogues, collectively referred to as plasma protein therapies. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. The therapies include clotting factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions.

PPTA welcomes the Commission's initiative to gather information about the experiences with the Paediatric Regulation and the lessons learnt. Please find below PPTA's comments on the consultation items.

**A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL**

**PART OF PRODUCT DEVELOPMENT**

**Consultation item No 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?**

Basically we agree, but it is extremely time consuming.

1. Frequently adult studies are finalized much faster than studies conducted in pediatric patients, leading to a delay in application and approval of an indication in adults (especially for the orphan population).
2. The stated main objectives of the Paediatric Regulation are to stimulate high

quality paediatric research and to increase the availability of medicines intended for children. As stipulated by the Paediatric Regulation it is mandatory that companies include paediatric studies into development plans for new medicinal products mainly intended for the adult population.

3. The substantial resources required may discourage development / innovation, especially since an expensive clinical development in paediatric subjects is required prior to initial approval in an adult indication (e.g. when the company starts to recover costs).
4. This also applies when the disease primarily occurs in adults and only few cases in paediatric population have been reported (orphan and ultra-orphan prevalence). Products developed for diseases primarily occurring in adults are delayed due to the pediatric requirements.
5. Existing experience provides many examples for reasons why a PIP could not be completed. The available data should be taken into account when a request for a waiver for the PIP is submitted.
6. Additionally, there is a gap, because the regulation is only prospective and does not “encourage” companies to systematically study existing (off-label) therapies in pediatric populations.

In conclusion, the Regulation does not pave the way for well-established medicinal products to extend information in the license (SmPC) to be used correctly in the paediatric population. The Regulation significantly delays new treatments (for adults) particularly in orphan indications.

## **HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.**

### **Consultation item No 2: Do you agree with the above assessment?**

It is acknowledged that the Paediatric Regulation aims to investigate medicinal products in the paediatric populations. However, the requirements of the Paediatric Regulation and the (possible) incentives and rewards are insufficient to encourage manufacturers to close the gap.

1. Scientific research in children requires multiple centers including sites outside EU and US, as it difficult to recruit children below 12 years of age in EU and US in a timely manner.
2. The PIP requirements support the development of age-appropriate formulations for children. However, the development program independent from the adult program is costly and time consuming. A flexible approach would reduce workload and costs.
3. Previously some paediatric subsets such as neonates were generally not included in clinical trials and no data were available resulting in off-label use of medicines in the youngest population. Experience has shown that recruiting neonates usually takes much longer than for the other study populations. This special situation should not lead to delays in the approval for other age groups.
4. The PIP requirements do not result in decreasing the off-label use of medicinal

products when paediatric information is missing due to insufficient systematic research (especially in populations above the age of two years).

In conclusion, we agree that it is too early to judge, but the discrepancies between new medicinal products and well-established medicinal products are obvious. It can be expected that for new products substantial clinical research will be conducted, while for well-established products the Regulation does not provide incentives that would stimulate research in the paediatric population and thus decrease off-label use.

### **THE PUMA CONCEPT: A DISAPPOINTMENT**

**Consultation item No 3: Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?**

Companies can request PUMAs for medicinal products that are exclusively developed for use in children. However in many cases medicinal products are developed for adults first and followed by paediatric development. Consequently the PUMA concept does not apply.

1. The currently available incentives (e.g. short increase in duration of data protection) do not compensate companies sufficiently for the expected investments required to generate new data in paediatric subjects or to collect data regarding off-label use of products in paediatric subsets. There is no incentive for a company to re-open clinical development of an already approved therapy.
2. Additionally, PUMA has no impact on national reimbursement for older medicinal products. A company would receive no benefit on drug reimbursement as this is a purely national procedure and often independent from the Licensing Authority.
3. A revision of the incentives could stimulate research for orphan and ultra-orphan indications in paediatric population by academic research, SMEs and global pharmaceutical companies.
4. The 12 year market exclusivity period (Article 8(1) of Regulation (EC) No 141/2000) should be extended to 15 years for orphan indications in paediatric age groups in consideration of the duration of clinical trials in these indications due to recruitment issues. 15 years would provide sufficient time to recuperate the development costs.

Consequently Articles 36, 37, 38, 39, 40 of the Paediatric Regulation on rewards and incentives need better implementation in order to help companies developing medicinal products for use in the paediatric population.

## **WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS**

**Consultation item No 4: Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.**

The statement that the paediatric requirements as outlined in the Paediatric Regulation and requested by PDCO do not delay the development of new treatments in adults is in contrast to the experiences of PPTA member companies.

1. The paediatric studies should start early in the development after finalization of Phase I PK/PD studies in adults, which is far too early and finally requires several modifications of the PIP which extend the overall program and delays the completion of all data required for a MAA (both in adults and children). Paediatric studies cannot start in parallel with adult studies and there is reluctance by PDCO and national competent Authorities responsible for the clinical trial applications in Europe to include paediatric subgroups in Phase I clinical trials. The risk that an adult takes during a clinical study is significantly less than the development risks that a paediatric subject would take. EMA guidance recommends / requires that sufficient adult exposure is obtained prior to starting paediatric studies.
2. Additional non-clinical studies are often required prior to conducting paediatric studies (e.g. developmental toxicity).
3. For extension of indications of existing licenses the challenges to agree on a PIP with the PDCO might even prevent MAA in adults in terms of cost-effectiveness considerations

Given these points, it is obvious that a requirement for a paediatric study prior to approval in adults will significantly increase the timeline.

According to the clinical development guidelines for FVIII and FIX products, the EU requires a positive compliance check for an agreed PIP based on the clinical study report of a clinical study in paediatric PTPs for initial MAA. The US accepts an indication restricted to adults (and adolescents) for initial BLA. This has led/currently leads to delays in MAA filing in Europe (and thus availability of the product for European adults) in our members' experience.

1. To avoid delays in availability to adults the European guidelines should require that recruitment into the paediatric PTP studies (or more general within the PIP agreed studies) needs to be completed at the time of MAA and the data presented by clinical study report directly after approval. The indication would be restricted to adults while the product is investigated in the paediatric population. This approach would ensure fast access to both, adult and paediatric population.
2. The compliance report needed for the application for MAA causes an additional risk for the target submission date of the MAA, especially if there are unexpected delays in recruitment of paediatric subjects in the clinical trials. Consequently a request for modification of the PIP is required including sound

scientific and clinical justifications causing a delay between 6 and 8 months before requesting the compliance check. On the other hand the letter of intent to file a MAA through the Centralized Procedure is mostly submitted while the paediatric studies are still ongoing, which complicates the overall situation. The compliance check can take another 3 months only to be able to file an MAA which can be validated. This truly adds to a longer timeline and contributes to a potential delay of MAA for adult treatment.

In orphan indications the concurrent development of adult and paediatric formulations significantly delays the availability of new medicinal product for adults.

1. In orphan indications the number of studies and number of subjects which can be recruited is limited. Difficulties in recruitment of children (e.g. limited population size, vulnerable population) delay the availability of new therapies in adults.
2. Consequently an approach to include a limited number of adult and paediatric subjects in one single study could be chosen with a staggered approach of assessing data from adults before including paediatric subjects in order to provide sufficient safeguard for the paediatric population. Due to rarity of orphan conditions the combination of adult and paediatric population within the same study represents a reasonable and feasible approach to evaluate efficacy and safety. From our experience the PDCO is reluctant to accept the inclusion of children age 12-18 years in a phase I study which starts with administration of the product to adult subjects.
3. For indications such as thrombotic thrombocytopenic purpura (TTP) with both hereditary and acquired etiology, PDCO requests data to support both indications and does not accept the applicant's decision on development of one indication. A hereditary indication might result in reduced availability of a particular protein/enzyme, whereas the acquired indication might face challenges in regard of development of autoimmune antibodies. Consequently two independent development programs might become necessary, with different posology, mode of administration, sampling and tests etc. A PPTA member company filed an initial PIP application for the indication of hereditary TTP. However PDCO requested both studies for hereditary and acquired TTP to be included in the PIP requiring 2 independent developmental programs. Such an insistence and change of the proposed development program could delay both the availability of new medicines in adults and in paediatric patients.

Although there is an obvious public health need for development of medicinal products for orphan indications in adults, the overall velocity of the development is reduced by the need to comply at the same time with paediatric obligations. It should be ensured that in such cases either a flexible approach is followed or a deferral is granted.

**MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS**

**Consultation item No 5: Do you have any comments on the above?**

We agree with the observation that paediatric development is dependent on adult

development, often not taking the specifics of the paediatric population into account, especially for substitution therapy in orphan populations. To determine the correct dosage in children data on kinetics in the paediatric settings should be generated, instead of reproducing the adult efficacy program in a smaller group of children.

1. In one case for the indication treatment of hereditary TTP the PDCO did not accept the inclusion of adolescents in a Phase I study although a staggered approach was proposed.
2. It is true that the paediatric development is dependent on the adults' development program not only for ethical reasons. The industry fully supports the requirements and obligations of the paediatric regulation but it seems that the required submission of a PIP during early product development is missing the point. This is simply not in line with one of the objectives of the paediatric regulation "... not to delay the authorization of medicinal products for other age populations".

We would respectfully propose to change the regulation to allow sufficient time for the generation of high quality data in adults first without requiring several Requests for modification of agreed PIPs as well as not delaying the submission of MAAs for other age groups – adults and elderly. A potential proposal could be that the approval of a PIP is mandatory before submission of the MAA for other age groups. The paediatric program needs to be completed within an agreed time point after the granting of MA (extensions must be handled via RfM). If the applicant does not fulfill the requirements of the paediatric regulation the license might be suspended until the required data have been provided.

## **THE BURDEN/REWARD RATIO —A BALANCED APPROACH?**

### **Consultation item No 6: Do you agree with the above?**

We disagree, because the possible extension of 6 months of the SPC is only of interest for applicants who have a patent in place. The burden for all companies is not balanced by the possible rewards.

1. The regulation does not bring any benefit for companies who are producing medicinal products intended for paediatric use.
2. Only applicants who have a patent in place might slightly benefit from an (possible) extension of 6 months of the SPC if the paediatric program has been completed in compliance with the granted PIP. 6 Months extension of data exclusivity does not allow a company to recoup any meaningful portion of the expenses required to conduct a paediatric study.
3. The imbalance is even higher if the product is not intended to be marketed for the paediatric population. The additional burden of clinical trials in children of all age groups and approval of indication for children does not have any impact on reimbursement which is purely national and often independent from the licensing Authority.

**ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION**

**Consultation item No 7: Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?**

1. So far it seems that only the authorities might benefit from the enormous number of study reports and provided data from “older clinical studies”. Articles 45/46 do not necessarily support public interest in product development in all ICH paediatric age groups without subjecting the paediatric population to unnecessary clinical trials.
2. Especially for orphan indications, both industry and health care professionals are interested in any clinical experience and documented cases available in order to offer potential (new) treatments to patients.
3. Articles 45/46 might have helped to compile paediatric data from older clinical studies. However it has not sufficiently led to inclusion of paediatric information in Core SmPCs or indication specific guidelines.

There should be joint efforts by regulators, health care professionals and industry in collecting as much paediatric data as possible e.g. databases, assessment reports to compile information on experience with medicinal products in paediatric age groups.

**LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED**

**Consultation item No 8: Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?**

1. National competent Authorities should develop strategies to encourage healthcare professionals to support development of medicinal products for all paediatric age groups. National networks for pediatric research, which exist in some European countries or are under development, e.g. Austria, have an important role in engaging pediatricians in clinical research. These networks should also be linked on an EU wide level and establish EU wide registries, which is specifically important for small patient populations.
2. Healthcare professionals function as link between the manufacturer developing new medicines and patients. It is their part/responsibility to discuss with patients/parents benefits and risks of an investigational medicinal product. This is a particular challenge for medicinal products that are still under development and have not passed authority review and received an approval.

## **CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED**

**Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?**

1. The overall time for initiation, the recruitment of the study and the conduct of paediatric studies is significantly longer than for adults.
2. The conduct of studies including both adult and paediatric age groups are not supported by PDCO especially for early clinical phases. This is a special challenge for extremely rare conditions (ultra-orphan indications). Since the Paediatric Regulation already requests the submission of a PIP when only limited data in adults are available, additional discussions and Requests for Modifications are required if the timelines in the initial PIP have been set too tight – or at a too early stage of development.
3. It shall be noted that while applicants have to plan years ahead straight unforeseeable things are likely to happen during product development that require modification of study designs and timelines especially in the paediatric population. This could lead to significant delay in the approval of a MAA for adult patients as clinical trials incorporating the various paediatric age groups as well as the compliance check might be delayed. Consequently the availability of medicinal products for unmet medical needs (e.g. orphan indications) would be delayed due to challenges with national clinical trial applications, recruitment and timelines committed in the PIP.
4. The PDCO is a committee within the EMA that influences the design of clinical trials. However clinical trial applications in Europe are subject to national approvals. As a consequence companies have to defend and discuss clinical design as agreed in the PIP even if company was reluctant to accept PDCO proposal in the initial PIP application.
5. Parents are reluctant to let their children participate in a clinical trial if an established treatment is available.

## **UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS**

**Consultation item No 10: Do you have any comments on this point?**

In the course of the development of new medicinal products evidence can become available that a PIP cannot be completed. Unfortunately, there are examples where this evidence was already available a waiver was requested, but declined. Despite the available evidence a PIP had to be submitted to fulfill the requirements for the MAA for adults. Regulatory Authorities and manufacturers should have the opportunity to assess these cases for their decision making processes.

It would often seem to make more sense to submit PIPs at later development stages (e.g. after phase 2 data) than after phase 1 data are available in adults, especially for NCEs. Biologics for substitution therapies may submit a PIP earlier as efficacy data are often generated early in the process.

## **SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED**

**Consultation item No 11: Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union?**

In principle we agree, but there are still limitations in exchange of expertise with stakeholders other than Regulatory Authorities, such as manufacturers or Medical Societies.

## **ANY OTHER ISSUE?**

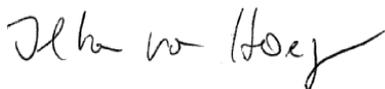
**Consultation item No 12: Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?**

The Paediatric Regulation is important to support and encourage the development of medicinal products for paediatric use, but from a manufacturers' point of view there is still room for improvement:

1. The requirements should be reviewed whether they add significantly to the safety of pediatric patients.
2. The requirement to conduct these studies prior to a MAA should be revised to allow a flexible approach and avoid delays introduction of a needed therapy in the adult population. In view of limited resources a PIP could be waived if substantial clinical experience is available (product class specific e.g. immunoglobulins).
3. There should be appropriate incentives for manufacturers of established medicinal products to conduct studies in the paediatric population.
4. Clinical data from "older clinical studies" where low number of paediatric subjects were included should be reflected in SPCs of well-established medicinal products
5. More paediatric studies should be deferred to after MA, to allow availability of the new treatment for the adult population and not delay the MA for adults.

We hope that you will find our comments constructive and helpful. We remain at your disposal, should you have any questions or need further clarification.

Sincerely Yours,



Dr. Ilka von Hoegen  
Senior Director, Quality and Safety