European Society for Developmental, Perinatal and Paediatric Pharmacology

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PCPD/12/01 — Public Consultation on paediatric report
Response to the public consultation related to the paediatric regulation

On behalf of the European Society for Developmental, Perinatal and Paediatric Pharmacology (ESDP)

Background of the responder

The ESDP is an independent organization with the objective to promote developmental pharmacology and therapeutics, whether fetal, perinatal or paediatric, in any matter appropriate to the purpose. The society was founded in 1988, and its members are professionals who are engaged in scientific research and/or clinical therapeutics or who have conducted basic or clinical research on the association's purpose. Our response to the public consultation will likely reflect an academic background that is not necessary similar to, but that is complimentary to other stakeholders (e.g., industry, governmental, patient organizations, or competent authorities).

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?

We agree that the paediatric regulation has stimulated paediatric development in the EU. It is, however, too early to state that paediatric development has become an integral part of the overall product development of medicines in the EU. With the results thus far, it may be justified to say that PIPs have become that, but it remains to be seen to what extent the com-

panies are willing to perform the studies of the PIPs and seek labelling for children.

HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE. Consultation item No 2 Do you agree with the above assessment?

We agree that the output of the currently completed paediatric investigational plans with subsequent authorisation is still too early to judge. There is, however, a notifiable increased international collaboration on the European level to facilitate clinical research, clinical pharmaceutical care, and the development of advanced *in silico* PK/PD models.

IN TERMS OF OUTPUT, THE PUMA CONCEPT IS A DISAPOINTMENT. 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?

In fact, the PUMA has not yet been successful and we consider it unlikely that PUMA will become more attractive in the coming years. We consider the PUMA to be of less importance than the incentives/requirements/rewards that concern new medicinal products and the pursuit of developing new ways to provide incentives for medicines of primary interest for children, rather than for adults.

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 absence of delays in adult applications was an essential part of the paediatric regulation. This might be an argument in support of the current practice to organise the first contact with the Paediatric Committee at the end of the phase I study among adult volunteers.

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?

Yes, there is the dependence of paediatric development upon adult development rather than paediatric needs. Therefore, new approaches must be

found to increase the development of the medicines that are primarily needed by the paediatric population.

THE BURDEN/REWARD RATIO —A BALANCED APPROACH?
<u>Consultation item No 6:</u> Do you agree with the above?

A thorough analysis of the burden/reward ratio of the European setting needs to be conducted in a proper timeframe in order to judge this balance.

<u>Consultation item No 7:</u> 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?

We agree that such a collaborative effort indeed generates additional information. However, data, which is important, should be in labeling and Summary of Product Characteristics (SmPCs). Those are the only places where such data is easily and effectively available for the prescriber. The hard work of the regulatory assessments is largely wasted, unless means are found to include important information in labelling/SmPCs. Certainly, the means to do that should be found.

<u>Consultation item No 8:</u> 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?

Off-label use is not simply a question of information. Off-label use has dominated paediatric prescribing because it has so often been the only option. Starting in medical school, generations after generations of pediatricians and other paediatric prescribers have had to adapt to an “off-label culture”. The situation has not yet significantly changed (as stated in the report item No 2), so how could the medical practice have already changed? The problem is not one of information, but of changing practice. A change of practice is not achieved by the provision of information; appropriate measures (i.e., educational interventions that have been shown to be effective) have to be instituted before a change of practice can be expected.

<u>Consultation item No 9:</u> 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?

As stated earlier, the real increase in the number of paediatric trials has yet occurred, so it is too early to make conclusions on problems or a lack of them. However, it is worth noting that networks have received too many proposals for clinical trials that have been badly planned or even unethical.

UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS <u>Consultation item No 10:</u> Do you have any comments on this point?

See item 1 and item 4.

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

It would be more appropriate to say that paediatric regulation has contributed substantially to an increase of paediatric expertise in the EU. Calling the current situation an establishment of a comprehensive framework of paediatric expertise in the EU is a gross overstatement. Europe is still far away from a comprehensive framework of paediatric expertise when it comes to the development and scientific study of paediatric medicines. Key problems are the short and limited experience and lack of theoretical knowledge of many of the new experts (i.e., including many members of the Paediatric Committee). The evidence suggests that the development in the EU has been more a crash-course building of minimum capacity to manage the new challenges than an establishment of expertise. Insufficient opportunities for high-quality capacity building are available, and environments where experience can be gained under appropriate supervision/mentoring are scarce.

<u>Consultation item No 12:</u> 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?

It is becoming quite apparent that if the PIPs with deferrals really lead to the clinical trials that have been planned, as is to be hoped, then the available infrastructure of networks and centres that are able to perform high-

quality studies within the EU is insufficient. The infrastructure aspect of building research capacity was discussed during the development of the Paediatric Regulation, but no solution whatsoever was proposed (i.e., EnprEMA is not infrastructure). The building of the European research infrastructure for paediatric clinical trials was left completely to the discretion of the members' states, with the result that it has, with the significant exception of the UK, been ignored. The experience from EnpEMA has shown that such infrastructure cannot be built to sufficient levels to meet future needs on the basis of revenue from industry-sponsored trials, simply because such income will only become available when studies are performed. Part of the success of the U.S. paediatric legislation can be assigned to the early creation of an infrastructure in the form of PPRUs. The success of the UK MCRN also documents the value of developing a good, timely infrastructure.

While it can be said that the paediatric obligations have had no impact on timelines in adult development, including marketing authorization, however, it becomes increasingly evident that many new medicines that likely fill important paediatric needs will become available with regulatory approval for children, and particularly newborns, after long delays, if at all. It is easy to get the impression that too many too long waivers have been granted, probably with the good intent of preferably erring on the safe side, but with many children suffering and even dying while waiting for the new innovative treatments. At this point, it is certainly too early to make a judgment, but then it is also already too late for many paediatric patients.