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European Commission
DG SANCO, Unit D/5
Mrs. P. Brunko

Email: sanco-pharmaceuticals-D5@ec.europa.eu

Your letter	Your reference	Utrecht, 27 November 2012
Casenumber	Our reference	
Handled by B. van Elk	Telephone (direct) +31882248072	

Re:
Public consultation on paediatric report (PCPD/12/01).

Dear Mrs. Brunko,

Please find attached the response on the public consultation regarding the paediatric report on experience as acquired as a result of the application of the paediatric regulation on behalf of the Medicines Evaluation Board of the Netherlands.

Yours sincerely,

A.A.W. Kalis
Executive Director of the Medicines Evaluation Board in the Netherlands

GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION

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 do agree that the Paediatric Regulation has paved a way in order to have safer medication. The same holds for proof of efficacy. Ultimately this will lead to less unauthorized and off-label use of medication in the paediatric age ranges. However, remarks can be made. The most prominent remarks that can be made: 1. Only new drugs benefit substantially from the regulation, whereas the older drugs are not assessed systematically from a full development pharmaceutical / pharmacological point of view.2. For development of new formulations for drugs under protection of patents / certificates the regulations is a hurdle due to the necessity to test the product for all at that moment already approved indication and might limit the willingness to develop such formulations. 3. The application of PIPs according to the condition / indication of new medication, hampers development in conditions / indications not indicated by the applicants, which resulted in various cases to loss of sound drug development in relevant indications. In this respect also specific paediatric points , growth and development, have to be put forward. Several inter-cellular and intra-cellular processes are driven by mechanisms, which are not active during adulthood. However, the same drivers and/or targets are often not silenced, but are at later age involved in other processes. Focusing at only the adult processes certainly eases applications for an opinion by the PDCO (either class waiver or regular PIP) and eases the way to go for an application for marketing authorization at the CHMP, but will neglect potential paediatric developments as indications / conditions specific for paediatrics might be too laborious(expensive) to work out. To conclude the applications according to condition / indications results a reduced number of drugs assessed for children for relevant indications.

Consultation item No 2: While the Paediatric Regulation has led to a certain amount of new authorisations that include paediatric indications, the regulatory instrument is recent and the data does not provide a sufficient basis for a comprehensive review. It will probably take at least a decade before the regulation can be judged in terms of its output. That said, it will always be a challenge to establish appropriate benchmarks for comparing off-label use with and without the Paediatric Regulation. Do you agree with the above assessment?

We do agree that the outcome can be judged in output later on. At this moment the number of studies can be seen as interim surrogate endpoint. Next surrogate endpoint to be used in the number of studies with positive compliance checks and ultimate marketing for children approved by CHMP.

Consultation item No 3: In terms of output, the PUMA concept is a disappointment. 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?

Indeed the outcome of the PUMA procedure is disappointing. A hurdle is the discrepancies of set-up of studies / development plans between the studies already approved in the FP7 subsidiary granting and the discussion at submitting the same studies to the PDCO. Lifting this hurdle might result in a (small) increment of PUMAs finalized and discussed at the CHMP or national level.

A major point of concern is that the PUMAs assessed are only not reflecting the data as given in the Priority list of off-patent medicine. Both in respect to indications and formulations the outcome is poor. As such the ultimate aim of the Paediatric Regulation can in this respect be designated as more or less "orphan".

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.

In the optimal situation the PIP application should be sent in at the moment of finishing phase 1 studies in adults. However, in many cases the applications are handed in later and even shortly before to go to CHMP. In case a negative opinion is issued by the PDCO a delay in submitting the dossier to CHMP or the national authorities is delayed.

Consultation item No 5: It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system. It aims to ensure that every innovation and every new product is screened for its potential use in children so that over time there will be a significant increase in the number of products for which specific paediatric data is available. Do you have any comments on the above?

This question refers to the points already addressed at consultation item number 1. The application of PIPs according to the condition / indication of new medication, hampers development in conditions / indications specific for children and not indicated by the applicants, which resulted in various cases to loss of sound drug development in relevant indications. There is increasing knowledge on the pathophysiology of deregulation in case of disease. In oncology clear examples can be put forward; such as tyrosin-kinase inhibitors in CML and GIST, retinoids in acute promyelocytic leukaemia. In non-malignant diseases the upcoming of exon-skipping agents in e.g. Duchennes disease and cystic fibrosis are clear examples.

Consultation item No 6: At the same time the Paediatric Regulation introduced a number of incentives intended to offset the additional burden, at least partially. One of the main incentives is the 6-month extension of the Supplementary Protection Certificate. While it is too early to assess the economic impact of the rewards — a topic which will be covered in a second Commission report due in 2017 (Article 50(3) of the Paediatric Regulation) — the European Medicines Agency and its Paediatric Committee have made acknowledged efforts to simplify the regulatory process wherever possible and within the limits of the regulatory framework. In addition, information is published systematically and Questions and Answers documents are updated for frequently asked questions. Do you agree with the above?

No comments

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?

The amount of evidence on efficacy and safety is limited for studies under article 45. The number of additions /modification to the indication section of the SmPC should be balanced against the impact of the changes. A balance should be made in respect to efforts and outcome should be discussed. MEB feels that based on experiences this balance is currently negative.

For studies under article 46 the assessment are part of regular assessment of studies for currently marketed products and can be seen as standard procedures for national agencies.

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?

We do agree with the statements that healthcare professionals should be more aware on information of medical products. This problem should indeed be solved at the national level. Although the commission is specifically requesting an opinion in relation to the Paediatric Regulation, the point raised is a more general one and applicable for all age ranges.

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?

There is a need to indicate how many participants in trials with a caucasian – European background included in PIPs in order to be relevant for the population in Europe in respect to pharmacogenomics. The number of trials done outside the EEA, as given in the report is of less value in respect to safety and efficacy.

Consultation item No 10: In terms of output, unnecessary efforts involving the compilation and screening of paediatric investigation plans are noted. On the other hand, early submission of and agreement to the paediatric investigation programme is necessary for the paediatric development to fit smoothly into the overall product development. Do you have any comments on this point?

PIPs are requested at the moment of finishing phase 1 studies in adults, however in many cases PIPs are submitted at later instances. Even PIPs with studies, which a full completion of the paediatric development are discussed at the PDCO. The data on the number of modifications in relation to the phase of adult development are in part indicative for the inappropriateness of timing of application of PIPs. Although early discussion at the level of the PDCO are valuable, a staggered approach could be adopted. Initially assessment based on the major outline of development is warranted. During paediatric development a further elaboration of studies in agreement with the PDCO could be considered.

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?

There is indeed an important initiative coordinated by EMA. However, the construction of such a framework needs much time and efforts. Currently no opinion can be adopted on the success of establishment of such an framework.

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 points of concern and improvement are mentioned above.