Directorate-General for Health and Consumers

Unit SANCO/D/5

BE-1049 Brussels

Ghent, November 26, 2012

Dear Mr/Mrs,

Please find below the replies to the Public Consultation on the Paediatric Regulation, of the Department of Paediatrics of Ghent University Hospital (Belgium). These comments were stated after consulting our staf members, which are all health professionals. We do not object to the publication of our contribution.

Yours faithfully,

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Consultation item No 1: A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

We agree that the Paediatric Regulation has paved the way for paediatric drug development: it has legalized paediatric clinical trials. Though, we have two major remarks:

- In our understanding, medicines for children can be subdivided in three main groups:
  1. Drugs for which the paediatric indication is similar to the adult indication;
  2. Drugs, prescribed in orphan diseases and
  3. Drugs, prescribed in specific paediatric diseases which differ from the adult indication (for instance, ACE-inhibitors are investigated thoroughly for essential hypertension and unfortunately to a much smaller extent in the population of hypertensive children with chronic kidney disease (secondary hypertension) which make the biggest part of the prescriptions of ACE-inhibitors in children.)

  The Paediatric Regulation has provided a framework for the first two groups but left the latter group in the cold.

- Another gap in the Paediatric Regulation is the lack of profound long term follow-up of children involved in clinical trials, especially long term follow-up focusing on the impact on growth and development.

Consultation item No2: HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE

Since the implication of the Paediatric Regulation in 2007, there has only been a slight increase in the number of paediatric trials. We agree that it's too early to judge on the result of these as this process of paediatric drug evaluation takes a decade to finalize. Meanwhile, off label use remains a problem.

Consultation item No3: THE PUMA CONCEPT: A DISAPPOINTMENT

Ten years of data and market exclusivity is not an appealing incentive for enterprises as the paediatric drug market is too small to be economically attractive. We can prove this statement with the experience that good pediatric formulations of off-patient drugs (for instance oxybutinin oral suspension or penicillin oral suspension) unfortunately have been withdrawn from the market in the past because they bring little income for the industry.

Academia lack facilities to set up good multicenter pediatric clinical trials as a part of a paediatric investigational plan for a Paediatric Use Marketing Authorisation. The 10 years of exclusivity is not a good incentive for the academia.

Consultation item No4: WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS

The concept of deferrals prevents delays in the processing of adult applications. On the other hand, we stress that efforts should made to start the trials within the paediatric investigational plan earlier in this process. This will enable the industry to carry out pediatric clinical trials in a more profound way and will provide time for good long term follow-up in children before the marketing authorisation is provided. The timely start of the trials can be only executed when the initial

paediatric investional plans are of good quality and based on a combination of adult phase I data and good preclinical data for the pediatric population.

Consultation item No5: MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

The Paediatric Regulation concentrates on the needs in the adult population while we especially need clinical trials for drugs prescribed in specific paediatric indications. We also have to mention that trials set up to prove the dose-respons relationship within a PIP do not suffice to provide good dosing guidelines as paediatric dosing might be sex-, size-, age- and maturation-dependent. From a pharmacodynamic point of view, we need better use of surrogate parameters to evaluate the efficacy of drugs used in children.

Consultation item No 6: THE BURDEN/REWARD RATIO – A BALANCED APPROACH?

The industry stakeholders will be able to answer this question, in the future.

Consultation item No 7: ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

Transparancy is still a problem in paediatric drug evaluation. When checking for currect or finished trials with a given drug, an investigator should check the public databases (Medline, Web of Science), the article 45-database, the database of opinions and decisions on paediatric investigational plans, etc. while awaiting the public accessibility of the EudraCT-website.

There is little incentive for academia to perform secondary analysis of existing data from pediatric trials. Publication of results of secondary analysis in good journals is rather usual.

Consultation item No 8: LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Daily clinical practice remains the primary task of the health care professional. Combining this task with research is difficult. Moreover, funding of research is currently focused on fundamental (genetic and immunologic) research while it is almost impossible to receive funding for clinical (drug) research.

Consultation item No 9: CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

We experience that current clinical trials, which are part of a paediatric investigational plan, have recruitment problems. Consequently, site are more and more situated in developing countries. This might hinder a good follow-up of the children who were involved in the trials.

The Paediatric Regulation deals with the ethical, financial and physiological burdens of pediatric clinical trials but the practical burden remains for improvement. Moreover, the combination of requirements of the PDCO and FDA can render the trial even more difficult to execute.

Consultation No 10: Unnecessary efforts? Non-completed paediatric investigional plans

We regret that paediatric investigational plans can be stopped when the corresponding adult development is stopped. By doing so, the investigation of the drug in specific paediatric indications might also be halted.

Consultation No 11: Sophisticated framework of expertise achieved

The European networks have enlarged the expertise and the alerting to pediatric clinical trials. Though, the subdiscipline networks should be expanded.

Consultation No 12: Any other issue?

Education in paediatric clinical pharmacology is scarce in Europe. Although the GRIP network has taken initiative to construct a good network for education in paediatric clinical pharmacology in Europe, it remains difficult for health professionals to enlarge their knowledge on specific paediatric pharmacology topics (such as pharmacokinetics, knowledge on the ethical and legal aspects of this research, etc).