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COLLEGE
TER BEOORDELING VAN
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MEDICINES
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BOARD

To DG Health and Consumers, Unit Sanco

Sanco-pharmaceuticals-D5@ec.europa.eu

Your letter	Your reference	Utrecht, 2 December 2013
Casenumber	Our reference	
Handled by H. van den Berg	Telephone (direct) +31882248346	

Re:
PCPIP/13/01-Public consultation on PIP guideline

Dear Sir, Madam,

Enclosed please find the reaction of the Medicines Evaluation Board in the Netherlands regarding the public consultation on the PIP guideline.

Yours sincerely,

Prof.Dr. H.G.M. Leufkens
Chairman

Public consultation on the paediatric regulation No 1901/2006

Comments from the Medicines Evaluation Board, the Netherlands.

Introduction
The Netherlands welcomes the public consultation of DG SANCO on the regulation on the paediatric regulation and the possibility to provide feedback.

In Response to consultation item No 1: Do you have any comments on the format and content of applications for agreement on or modification of a paediatric investigation plan and requests for waivers or deferrals?
The paediatric regulation is issued with the aim to facilitate the development and licensing of (better) medicines for children and to ensure high-quality research of the development of medicines for children within the European Union. Considering that the mode of action is conceptual for investigation of conditions and indications, important unmet needs for treatment in paediatric disease stay uncovered. As a result the currently agreed PIPs do not deliver sufficient-enough data to asses the fundamental issues in various paediatric conditions / indications. The legal structure in the regulation should be better suited for the development and registration if possible conditions and/or indications were also based on the mode of action of the medicinal product.

Investigation on basis of mode of action is also severely hampered, due to the list of class waivers. Applicants for marketing authorization have access to the procedures at the CHMP based on requests mentioned in the list of class waivers. As a result products with a potential benefit, as based on the mode of action, are not investigated for paediatric use. It is advised to delete the condition / indication section mentioned in the list of class waivers.

Based on the legal requirements of the current Regulation, a paediatric Investigation plan (PIP) has to be assessed at the moment phase I / II trials in adults are finalized. The Regulation however does not leave options for manoeuvre for the PDCO if the data, obtained at a later date, would necessitate revision of the PIP. A staggered approach should be introduced in order to create the possibility, that based on newly acquired knowledge, the PDCO could request a modification on its own motion. Both PDCO and CHMP should be involved in such a procedure and the MAH could be granted a temporarily deferral for a PIP.

Consultation item No 5
In response to other issues which have not been addressed in the consultation items.
PUMA: The MEB would like to reflect on the new type of marketing authorization introduced by the Paediatric regulation, PUMA, to give an incentive for research of potential paediatric use of off label pharmaceuticals products. The MEB would like to underline the importance of the rational to avoid off label use, but to make sure that there is a real incentive for companies. The PUMA should not include all categories of ages for the indication but, based on well established use, enable the possibility to apply for a PUMA for only for 1 category of age. Currently, the applicants have to study all age categories, unless the provide evidence that in some age categories the product will not be effective. In case the product is effective in several age categories, the applicant might be confronted with a negative cost/ benefit balance and might decide not to start a PUMA. The provision should give the Marketing Authorisation Holders the possibility to apply for a specific age category.

Quality: From a quality point of view the MEB would like to point out that in general, this section is in accordance with the recently adopted CHMP Guideline on pharmaceutical development of medicines for paediatric use. In section 2.5.2.1 guidance is given on the relevant aspects related to the paediatric formulation development that are to be addressed in the PIP. Some examples are given on critical issues that should be addressed as part of this discussion. Although these critical issues to be discussed (lines 359-368) are just examples, they could benefit from some revision/additions.

Proposals for revision:

Section 2.5.2.1 General strategy

1. Line 362: 'potential issues in relation to excipients to be used in the paediatric populations'
   Proposal: 'potential issues in relation to excipients and their (foreseen) exposure levels to be used in the paediatric populations'

2. Lines 363-364: 'administration of the medicine to paediatric subsets (e.g. palatability, use of specific administration devices, ability to mix with food)'.
   Proposal to use the more general term 'patient acceptability' instead of 'palatability' in line with the Guideline on pharmaceutical development of medicines for paediatric use.

3. Lines 365-366: 'precision of dose delivery in the case of solid dosage forms, when breakable tablets are proposed for paediatric use'. It is noted that precision of dose delivery is not only a concern when breakable tablets are proposed, but may also be a critical issue for oral liquid dosage forms, parenteral dosage forms, etc. Proposal: 'precision of dose delivery and/or dosing accuracy should be addressed for any dosage form in respect to the (foreseen) paediatric dose and indicated target age range'.

Section 2.5.2.2 Outline of each of the planned and/or on-going studies and steps in the pharmaceutical development) for the pharmaceutical development.

4. Lines 380-381: 'Agency guidelines in this area should be consulted to decide which measures could be relevant'. It is felt that this is a crucial statement for pharmaceutical development that should rather be made already in section 2.5.2.1 on the general strategy in paediatric formulation development.