SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE

Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies

COMMENTS FROM TEDDY Network /Prof. Adriana Ceci (coordinator)

GENERAL COMMENTS

The TEDDY network of excellence is actively working in the paediatric field and encourages a constructive working relationship with all interested parties in order to speed up the final form of the this guideline for the implementation of the Paediatric Regulation.
At this purpose several activities has been undertaken. Several work packages were specifically addressed to these issues. So far the work of the TEDDY project has led to the submission of several detailed reports both to the EMEA's Paediatric Expert Group and to the Commission.
Based on our experience in paediatric research, please find below our comments/suggestions:

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
SECTION 1 1.1: General principles and format par. 4	It would be convenient to make some reference to the experience obtained with drugs used in non-interventional (compassionate) protocols ?	Include also collection of data derived by drug administered in children by non interventional studies, (GCP compliant), when available
SECTION 1 1.1: General principles and format paragraph 4	Please also add info on spontaneous adverse drug reaction reporting to the relevant clinical information. So far, mainly data from clinical trials are used.	Add info on spontaneous adverse drug reaction reporting to the relevant clinical information.

Date of transmission:

Submit all comments to: by email to peter.arlett@ec.europa.eu in word forma please.
Deadline for comments: <30 March 2007>
These comments and the identity of the sender may be published on the European Commission website unless a specific justified objection is received by the European Commission.

SECTION 1 1.1: General principles and format paragraph 5	It is stated that: *"Following an Agency decision on an request for a waiver or a paediatric investigation plan or a deferral this should be submitted to the Agency without delay with a proposal to modify the paediatric investigation plan together with a request for a waiver or deferral as appropriate"* It is also possible that EMEA firstly can become aware of new information which may have an impact on the same EMEA's decision (e.g. data from EUDRACT paediatric section).	Please specify that : *…. if new information, that is unknown to the Agency, becomes available which may have an impact on the decision of the Agency, a review of the plan, waiver or deferral should be considered.*
SECTION 1 1.2 PART A: ADMINISTRATIVE AND PRODUCT INFORMATION A.6 Regulatory status of the product inside the Community Paragraph A 6	The description of regulatory status should also include every reference to an Orphan status granted in the Community	Please add " including orphan status (detailing orphan authorisation and/or orphan designation), and refused applications in any EEA Countries or in third Countries"
SECTION 1 1.2 PART A: ADMINISTRATIVE AND PRODUCT INFORMATION A.6 Regulatory status of the product inside the Community pag 6	Among the details to be included in the description of the regulatory status, it should be also included details on formulations, besides "details of the authorised routes of administration" It should also be included whether for this drug there are fixed dose combinations	Please add "details of the authorised formulations"
SECTION 1	It would also be interesting to provide gender specific incidence	Add gender specific incidence rates

1.3 PART B: OVERALL DEVELOPMENT OF THE MEDICINAL PRODUCT INCLUDING INFORMATION ON THE TARGET DISEASES / CONDITIONS B.3 Prevalence and incidence in the paediatric population	rates B3 It should also be mentioned the burden of disease in countries outside Europe, especially in countries from where immigration is frequent and eastern European countries.	Add other Countries information
SECTION 1 1.3 PART B: B.4 Current methods of diagnosis, prevention or treatment in paediatric populations /paragraph 1	There might be differences for diagnosis, prevention and treatment methods available within the Community, among different countries, for the same disease;	The applicant should indicate the differences of these methods from the Community Standard, if any; should indicate and document the methods proposed. Maybe differences in prevalence/incidence can be explained by differences in tracing/diagnostic methods.
SECTION 1 1.3 PART B: B.4 Current methods of diagnosis, prevention or treatment in paediatric populations	The reference to ‘unauthorised’ treatment methods is not clear, not having a common understanding. The reference terms most used are ‘unlicensed’ and ‘off-label’ (see also D.1.5)	This should include unlicensed/off-label treatment methods…

/paragraph 1		
SECTION 1 1.3 PART B: B.5 Significant therapeutic benefit / fulfilment of therapeutic need paragraph 5 Paragraph 7	5° paragraph: it may be this is the moment which the Paediatric Regulation would be referenced to FDCD, specific for children Para 2: It seems sometimes difficult to provide comparison of the medical product subject to the MA with the current standard of care, if the standard of care is based on off label drugs. FDCD could be useful to treat important chronic disease (HIV) or prolonged disease (Tuberculosis) to increase efficacy, adherence and avoid the resistance emergence Moreover since for some fixed dose combination for antiretrovirals produced just by generic company and available only in some countries such India, South Africa, Thailand etc, it would also important to have such infos. It is too vague to say that "significant therapeutic benefit cannot be justified". This is a key point because it is not clear to me what will be the measures that will guarantee that a waiver/delay will be followed by pediatric studies.	Add c1) availability of FDCD: "Fixed drugs combined drugs": Specify criteria which justify waiver/deferrals.
1.5 PART D: PAEDIATRIC INVESTIGATION PLAN D.1 OVERALL STRATEGY PROPOSED BY THE APPLICANT FOR THE PAEDIATRIC DEVELOPMENT D.1.2 Selected age group(s)	Also important to analyse separately by sex More convenient a maturation levels classification in pre puberal and puberal stages.	1) D.1.2 Selected age and sex group 2) …such as gestational age, pubertal stage(s), according to Tanner classification, and renal function.

1.5 PART D: PAEDIATRIC INVESTIGATION PLAN **"RATIONALE FOR DOSE SELECTION"**	No mention is made to the rationale for dose selection. This is a major flaw in the document, in that it leaves investigators and sponsors without clear understanding about the need to consider functional differences associated with developmental changes and concentration-effect relationships as the basis for the justification of drug exposure (dose and treatment levels) in clinical studies.	Please add a heading on the **rationale for dose selection** in clinical studies, highlighting the requirement to consider function as the basis for scaling between or within groups. The current use of size or age as basis for dose adjustment is often not sufficient. A model-based approach using concentration-effect PKPD relationship should be encouraged for the purposes of characterising optimal exposure in clinical studies and provide appropriate dosing recommendation in the label.
1.5 PART D: PAEDIATRIC INVESTIGATION PLAN D.4 STRATEGY IN RELATION TO CLINICAL ASPECTS	Regarding the specification of clinical trials that need to be done, please also taken into account the importance of the effect of gender, especially regarding pharmaco-dynamic and pharmaco-kinetic studies	Please also add the effect of gender, especially regarding pharmaco-dynamic and pharmaco-kinetic studies
1.5 PART D: PAEDIATRIC INVESTIGATION PLAN D.4 STRATEGY IN RELATION TO CLINICAL ASPECTS /last paragraph	Measures to protect the paediatric population Ethical consideration should be mentioned	…. should be discussed taking into account the European ethical guidelines provisions
1.5 PART D: PAEDIATRIC INVESTIGATION PLAN D.5 PLANNED	At the end of the list it would be necessary to add Ethical issues	Ethical guideline compliance

MEASURES FOR THE PAEDIATRIC DEVELOPMENT D.5.4 Synopsis/outline of protocol of each of the planned or performed clinical studies or trials paragraph 2		

Please feel free to add more rows if needed.

TEDDY participants in this evaluation

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