MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS SANITARIOS

COMMENTS TO THE COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF APPLICATIONS FOR PAEDIATRIC INVESTIGATION PLANS.
SUBMITTED BY THE AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS (AEMPS), SPAIN

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?

AEMPS comments:
It is assumed that the content (and format) of the paediatric investigation plan (PIP) report done by paediatric coordinators at the EMA and PDCO members should reflect the data provided by Applicants in the submitted PIP application. In this regard, the current PIP summary report template includes the following items that, as expected, closely followed those of the Commission guideline.

Part A - Procedure for the assessment of the application

- Details of the medicinal product and overview of the application
- Regulatory information on completed clinical trials related to the condition and to the development for the paediatric population
- Regulatory status of the product
    - Marketing authorisation status inside the European Union
    - Marketing authorisation status outside the European Union
    - Refusal / withdrawal / restriction of a marketing or extension authorisation or application (inside or outside EEA)
- Regulatory advice on the development of the product

Part B - Overall development of the medicinal product

- Discussion on similarities and differences and pharmacological rationale
    - Similarities and differences of the disease/condition between populations
    - Pharmacological rationale and explanation
- Current methods of diagnosis, prevention, or treatment in paediatric populations
- Significant therapeutic benefit /fulfilment of therapeutic needs

Part C - Applications for product-specific waivers

- Overview of the waiver request(s)
- Grounds for a product-specific waiver
- Grounds based on lack of efficacy or safety
- Grounds based on the disease or condition not occurring in the specified paediatric subset(s)
- Grounds based on lack of significant therapeutic benefit

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Part D -Paediatric investigation plan

- Existing data and overall strategy proposed for the paediatric development
  - Paediatric investigation plan indication
  - Selected paediatric subset(s)
  - Information on the existing quality, non-clinical, and clinical data
- Quality aspects
  - Strategy in relation to quality aspects
  - Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development
- Non-clinical aspects
  - Strategy in relation to non-clinical aspects
  - Overall summary table of all planned and/or ongoing non-clinical studies
  - Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies
- Clinical aspects
  - Strategy in relation to clinical aspects
  - Overall summary table of all planned and/or ongoing clinical studies
  - Synopsis/outline of protocol of each of the planned and/or ongoing clinical studies
- Timelines of measures in the paediatric investigation plan

Part E -Applications for deferrals

The summary report is not an easy document to be read for those who are not familiar with the content of PIP applications. Even for those accustomed to it the PIP summary report is difficult to follow. In particular section D of the report seems unnecessarily complicated. In this regard the information provided in section *D.1.3. Information on the existing quality, non-clinical, and clinical data* that mainly refers to the work already done for adults may be incorporated in the corresponding sections of the paediatric development, e.g. if no specific formulations are intended for the paediatric population, this should be stated when the adult formulation(s) is(are) described and not in the following section after the non-clinical and clinical data in adults have been provided.

It is acknowledged that these comments refer to the PIP summary report template rather than to the Commission guideline but as both follow a similar format it seems relevant to highlight them.

It is also suggested that more emphasis is made in the guideline regarding the rationale for efficacy extrapolation from adults to children, an issue that is usually addressed in section B, subsection "Similarities and differences of the disease/condition between populations". In this section appropriate arguments should be given for extrapolation of efficacy. Cross-reference to the "Concept paper on extrapolation of efficacy and safety in medicine development" (EMA/129698/2012) should be considered.

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Regarding modifications on agreed PIPs the guideline should, perhaps, make more emphasis that Applicants need to submit the complete EMA Decision (i.e. including all key binding elements). Both modifications of agreed PIPs and compliance reports (see question below) are not stand-alone documents, i.e. their assessment is not possible in the absence of a complete EMA Decision.

Consultation item No 2: Do you have any comments on the operation of the compliance check and/or the compliance statement?

AEMPS comments:
AEMPS would like to highlight that for compliance check assessment the complete (i.e. including all key binding elements) EMA Decision on the PIP should be provided by Applicants. This, perhaps, should be reinforced in the guideline.

Regarding the standard sentences to be included in the Marketing Authorisation it is unclear for us whether the reference number to be quoted is the PIP number or the EMA Decision number. This, perhaps, can be clarified in the guideline.

Consultation item No 3: Do you have any comments on the assessment criteria for significant studies?

No comments on this particular question.

Consultation item No 4: Do you have any comments on the key elements of a paediatric investigation plan? Is it appropriate to list key elements in this guideline or should key elements only be specified in the individual decision of the Agency agreeing a specific paediatric investigation plan?

AEMPS comments:
It is unclear whether the items included in the Annex of the guideline are the only key binding elements to be stated in the PDCO opinion/EMA Decision. If this were the case it is noticed that route of administration, doses to be administered and length of treatment are not mentioned in the Efficacy and safety studies, an issue that should be reconsidered.

Currently, "Study duration" and "Stopping rule(s)" are part of the key binding elements included in the opinion. If they are going to be kept in the future it would be desirable to clarify that study duration is usually longer than study treatment (what is usually quoted in the opinion is study treatment) while stopping rules usually refer to withdrawal criteria. For the purpose of the check of compliance at the time of assessment of MAA by clinical assessors we would suggest that the standard terminology is used.

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