14-01-2018

Submission of comments on '< Reflection paper on the use of extrapolation in the 5 development of medicines for paediatrics>' (EMA/ 199678/2016/)

Comments from:

Name of organisation or individual
SIOPE – European Society for Paediatric Oncology

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	SIOP-E welcomes the Agency's Reflection paper on the use of extrapolation in the development of medicines for paediatrics. Cancer drug development is predominantly driven by adult cancer needs but many of the drugs in development have potential application in the paediatric population. There are many situations where data already generated by studies in the adult population could be used in an extrapolation concept to avoid unnecessary replication of studies, allowing the studies conducted in the paediatric (target) population to be appropriately focused on addressing the clinically relevant gaps in knowledge. There are broadly two circumstances in paediatric oncology where extrapolation would be relevant; a) where the occurrence of a specific cancer spans the age range, for example this would include some forms of leukaemias including	

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	chronic myeloid leukaemia and acute myeloid leukaemia, some forms of lymphomas including Hodgkin lymphoma bone sarcomas, including osteosarcoma and Ewings sarcoma and melanoma. Where the disease is considerably less common in the paediatric age range, but biologically similar; i.e; chronic myeloid leukaemia or melanoma, the application of the extrapolation concept would avoid initiation of unfeasible efficacy studies that are inherently under-powered and uninformative and replace them with properly modeled extrapolations from existing (adult) data and formulation of a plan for more focused and informative data collection in the target population, for example age-range targeted PK studies. The second circumstance is where a drug's development has been for an adult cancer, but the drug's mechanism of action has scientific relevance in a paediatric cancer. Consideration of extrapolation of information gathered in the adult studies	

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	(clinical and pre-clinical), particularly on PK vs PD relationship and in relation to PD vs clinical effectiveness could be explored in an extrapolation concept to inform and focus the paediatric study designs. The concept of collection of follow-up data post-marketing authorization as part of a risk mitigation plan where long term events may occur in the paediatric (target) population that could impact on the risk-benefit is extremely welcome. The Reflection paper is sufficiently broad and inclusive to support the majority of circumstances where extrapolation could be of value. In subsequent supporting documents it would be helpful to see some worked examples as guidance for how these concepts could be practically applied. There may be a need for education and training programs to develop the expertise needed in this area.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 255-257		Comment: The assumption that growth and maturation effects are a potential risk needs to be considered in the context of the mechanism of the drug and pre-clinical models and additional studies in children to evaluate this risk may not always be relevant Proposed change (if any): generation of new safety data ~~are often likely~~ may be needed in the target population	
Line 340-341		Comment: Whilst we support this statement, it will be important within the extrapolation plan to avoid repeating unnecessary multiple dose escalations in a paediatric study when the therapeutic index would indicate that it is unlikely that unexpected toxicity would occur in the target population when dosed according to the source population data MTD. Proposed change (if any):	
Line 383		Comment: This is an important point: where possible, incorporating the PK/PD studies within a confirmatory efficacy study is an efficient approach but may require an adaptive trial design. Proposed change (if any):	

Please add more rows if needed.