EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 January 2018

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

Comments from:

Name of organisation or individual
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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)*
	IQWiG appreciates the opportunity to comment on the reflection paper. IQWiG supports the revision of the “Reflection paper on the use of extrapolation in the development of medicines for paediatrics” with respect to the aim of providing a framework for extrapolation as a methodology to generate evidence for regulatory assessment. The reflection paper could be further improved by adding and clarifying important issues, e.g., the consequences of a negative outcome of the extrapolation plan, the role of the comparator used in studies of the source population and in studies of the target population, the principles of evidence-based medicine to be followed when reviewing the data underlying the extrapolation concept, and ways to improve transparency.	

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)*
205-207		Comment: We agree that uncertainties underlying the extrapolation concept might not be fully resolved by the time of marketing authorisation. However, even if extrapolation is used, a positive risk-benefit ratio should be a prerequisite for marketing authorisation. Proposed change (if any): “It is possible that uncertainties underlying the extrapolation concept will not be fully resolved by the time of marketing authorisation despite a conclusion of efficacy and a positive risk-benefit ratio.”	
257		Comment: We agree that it is likely that the generation of new safety data will often be required in the target population. However, it remains unclear what kind of data is expected. In addition, it remains unclear as to how a risk-benefit ratio using data on benefits and harms from different sources can be determined. Proposed change (if any): Please specify the kind of data expected for safety and the determination of the risk-benefit ratio using data from different sources. This should be supported by detailed examples (see also next comment).	

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291-303		Comment: We agree that the need for data to be generated lies on a continuum, while some general scenarios can be outlined for illustration. For better understanding and illustration, generic examples covering the different scenarios should be added (similar to the generic example in the ICH E9 (R1) addendum on estimands). Proposed change (if any): Add generic examples. These examples should cover a broad spectrum of scenarios, and should include positive as well as negative outcomes of the extrapolation plan. Ideally, the scenarios should be based on real cases. The description should include the extrapolation plan itself, the results of the studies covered by the extrapolation plan, and the regulatory outcome.	
309-312		Comment: It should be clearly stated that when using surrogate outcomes, these have not only been validated in the source population, but are also valid for the target population. Proposed change (if any): “It may be possible to use surrogate or intermediate clinical endpoints for studies in the extrapolation plan, providing that they are also valid for the target population and that they account for the physiologic developmental changes in the paediatric population.”	

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415-418		Comment: One important aspect is omitted in the draft of the reflection paper: In cases where placebo controls are inappropriate for regulatory decision-making, the role of the active comparator has to be addressed in the extrapolation concept and the extrapolation plan. Proposed change (if any): Line 418: "… from baseline within two different patient populations. If different active comparators are appropriate for the source and the target population, the consequences have to be addressed in the extrapolation plan and the extrapolation concept. If active comparators do not differ between the source and the target population, the extrapolation of effects for the comparator has to be addressed."	

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438-446		Comment: We agree that in the case of a positive outcome of the extrapolation plan the use of extrapolation can be considered valid (line 440). However, it should also be stated that in the case of a negative outcome the use of extrapolation cannot be considered valid. Proposed change (if any): Line 442: "…, or for efficacy, cannot be confirmed, the use of extrapolation to support regulatory decision-making cannot be considered valid for the time being. The extrapolation concept needs to be updated to reflect …"	

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447-455		Comment: We agree that a structured plan to address uncertainties in the post-authorisation setting should be part of the extrapolation plan. It should however be added that a clear-cut hypothesis is also needed for post-authorisation data. In the case of a “negative” outcome of post-authorisation studies (e.g. the uncertainties cannot be resolved by these data) the marketing authorisation should be reconsidered. Proposed change (if any): Line 455: “… to document longer-term efficacy outcomes. The generation of post-authorisation data should follow a clear hypothesis and robust study design (e.g., a comparative study with an appropriate comparator and appropriate measures to avoid selection bias) to address the remaining uncertainties and assumptions underlying the extrapolation concept. Depending on the outcome of the post-authorisation studies, the marketing authorisation might be reconsidered.”	

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457-461		Comment: We propose that principles of evidence-based medicine have to be followed when developing an extrapolation concept. Proposed change (if any): Lines 458: “When developing an extrapolation concept and plan, … from the source and the target populations. The basic principles of evidence-based medicine should be followed, especially with respect to a systematic approach, completeness of data, assessment and consideration of bias, and transparency of reporting.”	
472-474		Comment: For marketing authorisations using extrapolation, the extrapolation plan (and its updates) and the data generated within the extrapolation plan are of equal importance. Therefore, the publication of the extrapolation plan should be mandatory. We propose to publish the plan as part of clinical study reports (e.g. as an appendix) of trials conducted within the extrapolation plan and also as part of the EPAR. Proposed change (if any): Line 474: “… to update – if appropriate – the extrapolation concept and plan. Independent of this, the (updated) extrapolation plan should be part of the clinical study report (CSR). The extrapolation plan will be published after marketing authorisation as part of the CSR and as an appendix to the European Public Assessment Report (EPAR).”	