9 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
ACRO (Association of Clinical Research Organizations)

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)*
	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes the draft Reflection Paper on the use of Extrapolation in the Development of Medicines for Paediatrics. ACRO congratulates the EMA on drafting a generally comprehensive document on such a complex subject. In addition to the specific comments noted below, ACRO	

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	has also identified the following general comments on the paper: • The term “prediction” is used throughout the draft document. However, generally, in statistics, “prediction” means a statement about data that, while not now observed, could, in principle, be observed; “inference,” in contrast, is making a statement about population parameters (where the “population” is the large set from which sample(s) could be taken) that are fundamentally unknowable (except in finite population situations). However, various lines of the reflection paper mention making predictions about the target population; this is confusing. We believe that “inference” is intended, instead, since the ICH E9 guideline on Statistical Principles for Clinical Trials (§2.1.2) indicates that clinical trials endeavour to make general statements about populations, not only about study subjects. • It would be helpful to explain how the extrapolation concept and plan, and their validation, will be embedded into (or positioned along with) current regulatory procedures; for instance, when should the extrapolation concept	

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	and plan first be submitted/presented to EMA (e.g. with PIP or during SA as needed)? Also, any recommended/specified time frame for amendments to the extrapolation concept and plan and their reporting might need to be presented if their submission and maintenance are correlated to regulatory procedures. • Though the extrapolation framework table could be referenced for documentation of the extrapolation concept and plan and their validation, it would be helpful if the EMA were to produce a related template and/or guideline for use by sponsors.	

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)*
33-38		Comment: ACRO congratulates the working party on developing a proposed definition of extrapolation that is broad and inclusive without being meaningless. However, we recommend adding clarification that the definition encompasses both extrapolation from adult to paediatric populations and between different age subgroups within paediatric populations. Proposed change (if any): Add clarification that the definition encompasses extrapolation from adult to paediatric populations, and between different age subgroups within paediatric populations.	
40-43		Comment: To ensure clarity, we recommend adding examples to show what is meant by “quantitative methods”. Proposed change (if any): Add examples to show what is meant by “quantitative methods”.	
47		Comment: Typographical error. Proposed change (if any): “Principle” should be “Principal”.	
58-64		Comment: ACRO recommends adding to this paragraph to explain where/how the extrapolation plan should be presented	

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		(e.g., should it be included within the PIP, or a reason given in the PIP for not providing an extrapolation plan?). Proposed change (if any): Clarify where/how the extrapolation plan should be presented.	
69		Comment: ACRO welcomes the flexibility in approach provided for in the Reflection Paper and agrees that an exhaustive list of methodological approaches is not necessary. However, we believe the utility of the document would be enhanced by including some examples of the approaches that could be used for various degrees of extrapolation. Proposed change (if any): Include some examples of the approaches that could be used for various degrees of extrapolation.	
83		Comment: ACRO recommends replacing the term “posology” with “frequency of dosing,” given the expected metabolic differences between adults & children. Proposed change (if any): Replace “posology” with “frequency of dosing”.	
101-103		Comment: This is also the case for medical conditions that affect children but not adults.	

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		Proposed change (if any): Add “or non-existent” after “completely different.”	
105		Comment: Since the phrase in parentheses includes antibacterial agents, “exposure” seems to refer to “exposure to the investigational product” (in which case further clinical trials will probably be obviated), rather than “exposure to the disease.” However, the reference is not obvious. Proposed change (if any): Clarify whether this “exposure” is the exposure to the investigational product, or the disease, or something else.	
111	Typo	Comment: Typographical error. Proposed change (if any): “Are” should be “is.”	
114	Typo	Comment: Typographical error. Proposed change (if any): “Obtain” should be “obtaining.”	
118	Typo	Comment: Typographical error. Proposed change (if any): “Population” should be “populations.”	
122	Typo	Comment: Typographical error. Proposed change (if any): “Requires” should be “require.”	
166		Comment: ACRO recommends that this sentence should be	

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		made clearer since areas where there are no gaps in knowledge should be highlighted rather than identified, given that they would support a more robust/complete extrapolation plan. Proposed change (if any): "……also **highlight** important aspects of the concept where gaps in knowledge do not exist and hence further data need not be generated".	
167-169		Comment: It would be helpful to provide actual examples where various gaps in knowledge (e.g., PK and PD) exist and the different extents of extrapolation that are recommended to be applied to them. Proposed change (if any): Provide actual examples where various gaps in knowledge (e.g., PK and PD) exist and the different extents of extrapolation that are recommended to be applied to them.	
178-181		Comment: This paragraph may appear to suggest that extrapolation to younger age groups may be relied upon to support interpolation to older groups; in other words, no paediatric studies may actually be required. It is not clear if that is the intention here. It may well be possible in some circumstances (e.g., for protein pump inhibitors, where a number of drugs are already approved in adults and children, and invasive end-points correlate well with PROs) and, if this	

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		is the intent, ACRO recommends that it is stated more clearly. Additionally, recognised age subgroups of the paediatric population should be defined by reference to the ICH E11 guideline (Clinical Investigation of Medicinal Products in the Paediatric Population). Proposed change (if any): Add a statement to clarify the intent of the paragraph, and refer to ICH E11 for definition of age subgroups.	
178		Comment: Typographical error. Proposed change (if any): “From” should be “to.”	
197		Comment: Typographical error. Proposed change (if any): “Rationale” should be “rational”.	
200		Comment: The sentence seems to be incomplete, or there may be a word missing. It is not clear what the sentence is trying to say. Proposed change (if any): Revise the sentence to ensure its meaning is clear.	
215		Comment: Typographical error. Proposed change (if any): Replace “relation” with “relations.”	

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240		Comment: Typographical error. Proposed change (if any): Replace “differ to” with “differ from.”	
243		Comment: The distinctions between Bayesian & frequentist statistics do not relate to the “precision of estimated effects;” estimates in either paradigm can be stated to any number of decimal places. Rather, Bayesian statistics (unlike frequentist statistics) can quantify certainties about population parameters. Proposed change (if any): Replace the text with “…for quantification of certainties about population treatment effects.”	
245		Comment: Given that there will be no single expert interpretation, ACRO recommends revising the text, as indicated below, to reference expert opinion instead. Proposed change (if any): Replace existing text with “…to elicit expert opinion and to integrate that opinion with the available information could be considered…”	
255-257		Comment: ACRO welcomes the recognition that the potential impact of drugs on growth, development and maturation may not be amenable to this approach. Proposed change (if any):	
264		Comment: It is not clear whether “source data” (which the draft does not define earlier) are data collected from the source population.	

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		Proposed change (if any): Clarify the origin of the “source data.”	
279		Comment: Typographical error. Proposed change (if any): Replace “needs” with “need.”	
306		Comment: Typographical error. Proposed change (if any): Replace “population” with “populations.”	
322-325		Comment: This sentence states “The benefit of a staggered approach across age groups, due to safety concerns or the need to have PK and PD information in older children before enrolling younger children, should be balanced against the need for timely access to a medicinal product even for the youngest age groups of the paediatric population.” However, the draft guidance on Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors published by the European Commission in June 2016 notes (correctly, in ACRO’s view) that “a ‘staggered approach’ (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended.” ACRO recommends that the current draft Reflection Paper should be aligned with the position of the expert group responsible for the Commission’s draft guideline.	

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		Proposed change (if any): Replace the statement with that developed by the European Commission's expert group.	
327-334		Comment: This section appears to be suggesting the conduct of mechanistic, non-efficacy trials in children. If so, this raises ethical issues and would result in studies which could be very challenging to enrol, due to parents being reluctant to give their consent. Proposed change (if any): The intent of the text should be made clearer, and the statement aligned with the ethical principles adopted by the expert group working on the European Commission guideline referenced above.	
351		Comment: The sentence seems to be incomplete Proposed change (if any): Change text to "…Every effort should be made to design and power the studies to meet their objectives."	
362-364		Comment: The underlying assumption here is that a dose of X generates a plasma concentration of Y and that produces a clinical response of Z, all of which can be confirmed in adults, and so the same relationships will be present in children. However, this assumption should be made only when there is compelling evidence that the same relationship exists in all age subgroups of the paediatric population.	

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		Proposed change (if any): Revise the sentence to read “For example, if based on the extrapolation concept the exposure-response relationship is established to be identical in adults and relevant paediatric subgroups, the objective of the PK study should be to identify the dose in different age groups that match the PK exposures that were related with clinical efficacy in adults.”	
378	Typo	Comment: Typographical error. Proposed change (if any): Replace “level” with “levels.”	
392-396		Comment: ACRO welcomes and fully supports this insistence on not artificially amending study objectives. Proposed change (if any):	
399		Comment: The EMA Guideline on the Choice of Non-inferiority Margin states “the most common aim of non-inferiority trials" is probably “to provide data to show that there is no important loss of efficacy if the test product is used instead of the reference.” Thus, the NI margin should be selected to support showing that “the test product is not substantially inferior to the reference.” If a NI margin is widened beyond such an “important loss of efficacy,” as seems to be suggested here, then the analysis might fail to show the lack of that level of inferiority. Proposed change (if any): Delete the reference to “widening a non-inferiority margin”.	

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412		Comment: It is not clear whether the “stratification” here refers to stratifying the randomization or the recruitment of patients, or (perhaps) both. Proposed change (if any): Clarify what “stratification” refers to in this context.	
415-418		Comment: The control treatment, and not only the investigational one, could be “active” (line 416). Additionally, FDA guidance on non-inferiority studies suggests that ratio measures of effect (odds ratios, risk ratios & so on) often provide a better basis for extending results of historical studies to a new NI study (less inter-study variability in treatment effects). ACRO recommends that the Reflection Paper should describe how the same principle applies to extending results from adult populations to paediatric populations. Proposed change (if any): Replace “active treatment” with “investigational treatment” in line 416, and add text to describe how ratio measures of effect can be applied to extrapolating results from adult populations to paediatric populations.	
419-421		Comment: ACRO recommends referencing the ICH E10 guideline on Choice of Control Group in this paragraph. Proposed change (if any): Add reference to the the ICH E10 guideline.	
451		Comment: It is not inevitable that less data will be generated in these circumstances. Even when more confidence exists in the extrapolation concept, more data might be sampled from	

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		the target population if, for example, those data are easily obtained. Proposed change (if any): Replace “inevitably” with “often”.	
454-455		Comment: Upon marketing authorisation, the “longer-term efficacy outcomes” of interest are population parameters (or future data), not sample statistics; hence, trialists cannot “document” them, but, at best, can make inferences (or predictions) about them. Proposed change (if any): Replace “to document” with “to substantiate trustworthy inferences (or predictions) about.”	
470		Comment: Not everyone reading the Reflection Paper will be familiar with acronyms commonly used within the EMA. ACRO therefore recommends that the acronyms (PDCO, SAWP, CHMP) should be defined. Proposed change (if any): Define the acronyms.	
475		Comment: Mechanisms presented under clinical response to treatment seem incorrect when considering the listed items along with those under the other categories. Proposed change (if any): It may need to be corrected as “Age-related **differences in** - applicability	

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		- validation of efficacy & safety endpoints”	
		ACRO thanks the Agency for the opportunity to comment on this reflection paper. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.	

Please add more rows if needed.