Submission of comments on Concept paper on the revision of the guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMA/CHMP/448599/2016)

19 July 2017

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 EMA's intention to update the current guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. ACRO supports this initiative to update the current guideline in the light of experience gained since it was published in 2006. ACRO fully supports the inclusion of the various points discussed in the Concept Paper. In addition to specific comments on the text (below), ACRO recommends that	

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	guidance on the following important topics should also be included in the updated guideline: • We recommend that the guideline should stress that the PK approach taken should seek to minimise the blood volumes required from each paediatric participant, with sponsors being encouraged to present Paediatric Investigation Plans (PIPs) which incorporate conservative approaches, e.g., micro-sampling and scavenged sample approaches. • We also recommend that guidance could usefully be offered regarding the number of data points which would be considered as sufficient, depending upon the model intended to be used. Alternatively, we suggest that sponsors could be required to justify the number of data points specified in trial protocols. • In some instances, knowledge of pharmacogenetic differences, which can affect exposure levels, may be required. However, the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in paediatric populations. ACRO therefore recommends that the proposed update should address situations where there may be differences in gene expression between paediatric and adult populations, between different paediatric populations, and within a	

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	paediatric population. • The current guideline notes that "If a similar relationship between concentration and clinical efficacy cannot be assumed, paediatric PK/PD (biomarker) data can be used to extrapolate efficacy. In this case, the predictability of the biomarker should have been documented. If this has been performed in adults only, its value for the paediatric population should be adequately justified." Given the increasing use of biomarkers in the development of medicinal products, ACRO considers this an important point and recommends that the updated guideline should include guidance on the evidence required to support use in a paediatric population of a biomarker that has been evaluated in adults. We also note that the US 21st Century Cures Act indicates (at §3011) that the timeframe for establishing a process for biomarker approval will be up to 5 years. Since paediatric medicines development is almost always necessarily global, congruence between the FDA and EMA requirements will be essential.	

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)*
40-51		Comment: The relationship between PK and efficacy has been clearly addressed and will be updated in the guidance, but ACRO also recommends greater discussion regarding the relationship between PK and safety. While there may be the assumption that efficacy can be achieved if paediatric exposures are comparable to adults, can the same be assumed for safety? Can the therapeutic window in adults be considered similar for paediatrics? We consider that these questions should be addressed. Proposed change (if any): Include more discussion on the relationship between PK and safety when extrapolating from adults to the paediatric population.	
42-43		Comment: ACRO recommends that consideration should be given to requiring the choice of scaling method to be justified in the PIP, enabling examination prior to clinical investigation. ACRO also recommends that the phrase "different paediatric subpopulations" should be accompanied by examples for clarity, and that consideration should be given to actively encouraging the inclusion of minors down to the ages of 14 or 12 in adult programmes, such that exposure in, arguably, the less vulnerable part of the paediatric population is available to inform subsequent investigation.	

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		Proposed change (if any): Explain that the choice of scaling method should be justified in the PIP, include examples to clarify the phrase "different paediatric subpopulations", and consider actively encouraging the inclusion of minors down to the ages of 14 or 12 in adult programmes, such that exposure in, arguably, the less vulnerable part of the paediatric population is available to inform subsequent investigation.	
44-45		Comment: In a previous Concept Paper (on the need for revision of the guideline on excipients in the label and package leaflet of medicinal products for human use, CPMP/463/00), the EMA wrote that "It is important to note that the safety of excipients can affect children differently than adults due to the ongoing organ development and incomplete maturation depending on the age." Given that no excipients have been certified for use in children, ACRO recommends that the use of excipients in investigational medicinal products intended for paediatric populations is discussed in greater detail in the current Concept Paper and resulting guideline, which might also usefully remind sponsors of the need to generate multiple formulations, e.g., elixirs and solid dosage forms, when the target paediatric patient group goes below 5 years of age. In addition, ACRO recommends that it would be helpful to include in the guideline a discussion regarding the choice of vehicle for drug administration (e.g. mashed banana, applesauce, pudding, etc.), for oral administration of pellets, mini-tablets, or other formulations.	

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		Proposed change (if any): Include greater detail on the use of excipients in investigational medicinal products intended for paediatric populations, and add a discussion on the choice of (non-excipient) vehicle for oral administration of products.	
59		Comment: Within the bullet, "Update the section on paediatric age categories" ACRO recommends including a discussion of relevant, new information regarding age-dependent changes in enzyme and transporter activity, as well as potential biomarkers, and how that information impacts the design of paediatric studies. Proposed change (if any): Include a discussion of relevant, new information regarding age-dependent changes in enzyme and transporter activity, as well as potential biomarkers, and how that information impacts the design of paediatric studies.	
		ACRO thanks the Agency for the opportunity to provide comment on this concept paper. Please contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.	

Please add more rows if needed.