5 October 2018

Submission of comments on the Draft addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/CHMP/187859/2017)

Comments from:

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 and supports the draft addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements. ACRO considers this to be a useful document that provides helpful guidance on the subject. ACRO especially welcomes the CHMP's recognition that, in some cases,	

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	only paediatric pharmacokinetic studies will be considered necessary to confirm the extrapolation of efficacy data generated in adults to paediatric patients, and the recommendation that, when supported by sufficient existing data, modelling and simulation of adult data may be sufficient to support dosing recommendations for certain paediatric age subgroups. Although it is not stated explicitly in the draft guideline, the overall impression is that, in some cases, a traditional pharmacokinetic study in paediatric patients is recommended to allow extrapolation from adult data in the absence of paediatric clinical efficacy studies. ACRO recognizes that the intent is to minimise the burden on the paediatric population and the number of paediatric patients involved in pre-authorisation clinical trials. However, it is often not practicable to recruit sufficient numbers of paediatric patients into traditional pharmacokinetic studies to assess the true interindividual variability required for interpretation of the results of these studies. For this reason, population pharmacokinetic data analysis from a larger number of individuals in well-designed population pharmacokinetic studies can be helpful in developing medicines for paediatric use. The use of population pharmacokinetic studies are not discussed in the draft guideline and, while noting that the referenced guideline on the role of	

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	pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004 Corrigendum) addresses the role of population pharmacokinetics studies, ACRO considers the absence of any reference to population pharmacokinetics studies in the current draft guideline to be a significant omission and recommends that an appropriate discussion be added. ACRO also recommends that the draft guideline should state clearly that it does not apply to the clinical development of antibacterial vaccine products, due to the special characteristics of these products and the importance of the state of development of the immune system in very young paediatric populations. Overall, ACRO considers that the proposed addendum is helpful in providing more specific guidance to sponsors of non-vaccine medicinal products and combines PK/PD considerations with a broad approach to new potential development strategies. We recommend that the addition of guidance for preclinical programmes and short-term clinical trials in the case of co-development of two or more agents should be considered. This should clarify if there is a need to show the antibacterial effect of each new agent as part of the paediatric plan.	

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)*
158-162		Comment: Research in neonates may not be relevant for all conditions and ACRO recommends that this is stated clearly in the guidance. Additionally, while ACRO recognizes that, when appropriate, PK data is required in neonates and cannot be extrapolated due to the rapid developmental changes in this group, the conduct of even single-dose PK studies in neonates is operationally challenging and raises profound ethical issues, as these trial subjects will receive no benefit. While acknowledging the scientific and medical rationale for such studies, the current linking of Paediatric Investigation Plan (PIP) requirements to adult marketing authorisation approvals can mean that drugs which are genuinely beneficial to adults and older children may be kept from the market pending neonatal data. Consequently, ACRO recommends adding the statement proposed below in order to indicate that the need for neonatal PK studies will not delay marketing authorisation approval in other populations, allowing new agents to be prescribed to patients shown to benefit from them while still encouraging neonatal exploration. Proposed change (if any): Revise the sentence in line 161 to read “pharmacokinetic data will need to be generated in neonates in almost all cases where appropriate owing to the rapid……”, and add a statement to the effect that the CHMP recognizes that the practical difficulties of performing PK	

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		studies in neonates often result in studies being performed over several years, and will therefore look favourably on requests for deferral for the completion of such studies.	
160		Comment: The word “the” is missing from the phrase “On other hand…” Proposed change (if any): The sentence should begin “On **the** other hand……”	
163-166		Comment: It is not clear how a sponsor would form suspicions of safety concerns in the absence of data. It would therefore be helpful to include some examples. Additionally, it would be helpful for the guidance to clarify whether existing PK data in similar conditions could be used if a study in one infection is considered supportive/pivotal to the use of the product in another indication. Proposed change (if any): Add appropriate examples, and insert an additional sentence between the existing two sentences, which reads “Alternatively, evidence already or concurrently generated with the drug under development in adult and paediatric populations with similar diseases or conditions could be used.”	
177-235		Comment: In ACRO’s view, Sections 5.1 and 5.2 of the proposed guideline are especially helpful to support the	

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		development of antibacterial medicines in the paediatric population. Proposed change (if any):	
274-277		Comment: In general, ACRO supports the statement that "There is particular concern regarding systemic exposures that may result from topical treatments in children below 2 years of age due to the uncertainties about the age at which the skin barrier function can be considered fully mature and the age-dependent larger ratio of body surface area to body weight which all predispose to an increased systemic absorption." It would be helpful, however, for the guideline to provide guidance on how such a situation should be addressed. However, as noted in our General Comments, it should be made clear that this guidance does not apply to studies with vaccines. In addition, ACRO's comment on lines 158-162 also applies here, and ACRO recommends adding the statement proposed below in order to indicate that the need for studies in this group of patients will not delay marketing authorisation approval in other populations, allowing new agents to be prescribed to patients shown to benefit from them while still encouraging neonatal exploration. Proposed change (if any): Add guidance on how this situation in children below 2 years should be addressed, confirm that the guidance does not apply to studies with vaccines, and add	

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		a statement to the effect that the CHMP recognizes that the practical difficulties of appropriate studies in this population often result in studies being performed over several years, and will therefore look favourably on requests for deferral for the completion of such studies.	
255-262		Comment: In ACRO's view, this paragraph is especially helpful to support the development of antibacterial medicines in the paediatric population. Proposed change (if any):	
290-367		Comment: In ACRO's view, Section 6.2 is especially helpful to support the development of antibacterial medicines in the paediatric population. Proposed change (if any):	
322-324		Comment: ACRO recommends that the guidance should state clearly that placebo control trials are not needed from age 6 months to 3 years. Proposed change (if any): Revise the sentence to read "It is considered that published data support acceptance of a non-inferiority trial design provided that the patient population is aged from 6 months to 3 years, has adequately defined AOM and the comparator is specified (a placebo controlled trial not	

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		required)."	
		ACRO thanks the Agency for the opportunity to provide comment on this Draft addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/CHMP/187859/2017). Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions at all.	

Please add more rows if needed.