12 September 2018

Submission of comments on Concept paper on preparation of a revised guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/75653/2018)

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 and supports the EMA concept paper on the preparation of a revised guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. ACRO agrees that the proposed revisions to the current guidance documents, described in section 4 of the concept paper, are important and supports them fully. There are three specific issues that ACRO considers	

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	require greater detail than outlined in the concept paper: • The concept paper notes the intent to update the guidance text to reflect the points of alignment agreed in recent meetings with the US FDA and Japanese PMDA, including non-inferiority margins. This is an extremely important factor in antibacterial medicine development, as the recognized effectiveness of products may change with time, due to alterations in resistance patterns and/or the development of new knowledge. Selection of successively less effective comparator agents can result, over time, in the presumed 'equivalence' of statistically and clinically inequivalent products. Measures to counter this often require large increases in the number of patients participating in clinical trials, leading to significant increases in the length of time required to perform clinical studies and significantly increasing the cost of clinical development to the point where (in some cases in the past) this has no longer been economically viable and has contributed to the antibacterial "drug lag". Current guidance on the clinical development of antibacterial medicines (EMA/CHMP/776609/2011) notes that "Sponsors may wish to propose alternative non-inferiority	

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	margins to those suggested (e.g. based on emerging methods for estimating the placebo effect). These proposals will be given due consideration according to the strength of the supportive evidence." ACRO considers that it is essential that flexibility based on scientifically sound evidence is encouraged in the planned revised guidance in order to maintain/increase the development of antibacterial medicines. • The concept paper does not mention any plan to update the text on clinical trial designs for demonstrating superiority of the test agent over placebo or an active comparator when this is considered necessary. The conduct of such studies with antibacterial agents is notoriously difficult and ACRO recommends revision of this aspect of the guidance in light of recent trends and experience, taking into account the practical and ethical issues associated with these studies. • In a survey of pharmaceutical industry professionals working on the clinical development of new antibacterial agents, the following four regulatory changes were rated as high impact in facilitating the development of antibacterial medicines (Bettiol *et al.*	

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	Antimicrobial Agents and Chemotherapy 2015, 59: 3695-3699): creation of new regulatory pathways, provision of regulatory guidance on pathogen-based indications for multidrug-resistant organisms (MDRO), conditional/limited-use approvals for MDRO based first on microbiologic surrogate endpoint data, and regulatory acceptance of external control data. ACRO recognizes that the creation of new regulatory pathways is outside the scope of the planned guidance (and is addressed in other EMA initiatives) but recommends that the proposed revision should expand current guidance on the subjects of pathogen-based indications for MDRO, limited-use approvals based on microbiologic surrogate endpoint data, and the regulatory acceptance of external control data. Additionally, given that both industry and regulators are looking to increase the use of real world evidence (RWE) in regulatory decision-making, it would be helpful if the revised guidance were to include recommendations on the use of RWE to examine safety and/or expand indications following the initial limited authorisation of an antibacterial medicine.	

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)*
		We have no comments on specific lines of text.	
		ACRO thanks the Agency for the opportunity to provide comment on this Concept paper on preparation of a revised guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/75653/2018). Please contact ACRO (knoonan@acrohealth.org) if we can provide additional information or answer questions.	

Please add more rows if needed.