Submission of comments on a Concept paper on a guideline on the evaluation of medicinal products indicated for treatment of influenza (EMA/CHMP/EWP/808940/2016)

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 develop guidance on the evaluation of medicinal products indicated for treatment of influenza. ACRO has no specific comments on the text of the Concept Paper. However, as the relevant science in this area is developing rapidly, ACRO queries whether the proposed guidance would be best presented as a reflection paper rather than, as proposed, a guideline. ACRO fully supports the inclusion of the various points	

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	discussed in the Concept Paper. Additionally, ACRO recommends that guidance on the following important topics should also be included in the planned guideline/reflection paper: • The inclusion of guidance for pre-clinical and early development of influenza medicinal products would be helpful to sponsors. • The addition of guidance regarding the inclusion of special populations (e.g., the elderly, immunosuppressed, etc.) in clinical trials would also be helpful to sponsors. • The inclusion of guidance regarding stratification of enrolment based on gender / age / risk population would also be very helpful. • The proposed guideline/reflection paper would be enhanced by statements regarding the use of placebo in influenza trials in general and in high risk populations specifically. • The planned guideline/reflection paper should describe the criteria that will be used in the European Union for the definition of high risk groups (ideally, given the global nature of	

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	medicines development, these criteria will be aligned with internationally accepted standards). • In practice, adolescents are frequently given the same dose of an influenza medicine as the adult population. It would therefore be helpful for the guidance to include a statement concerning safety in the adolescent population as well as in adults. • Currently, Oseltamivir is the most widely used anti-influenza medicine. However, there is a warning in the prescribing label in some countries that Oseltamivir is associated with neuropsychiatric effects including suicidality. ACRO therefore recommends that the planned guideline/reflection paper should establish a unified approach for the use of Oseltamivir as a comparator in clinical trials in EU. • In addition to the proposed discussion of the role of challenge studies in dose selection, ACRO recommends that the guidance should make clear that only challenge studies using adequately safety-tested challenge influenza strains should be performed, and provide guidance on the evidence needed to demonstrate safety of the proposed challenge strain.	

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	• Given the difficulty of differentiating the symptoms of influenza from those of other viral illnesses (e.g., the common cold), guidance should be included on the acceptable entry criteria for clinical trials prior to the availability of confirmatory laboratory test results. • Additionally, ACRO advises that recommendations should be included about the diagnostics of influenza for the confirmation of the diagnosis. The question here is whether it should be clinical only or whether confirmatory tests would be recommended. The most common test in current use is the Rapid Influenza Diagnostic Test (RIDT). RIDT has 100% specificity, but its sensitivity varies from 30% to 70%. Consequently, a negative RIDT result does not mean that the patient has no influenza. • Time to alleviation of symptoms has been commonly used as the measure of efficacy in studies of influenza medicines. However, patients with underlying chronic diseases may share some symptoms of influenza and which are worsened by influenza. It is therefore not clear whether this is also the appropriate endpoint for the severe or high risk of influenza complication population and so ACRO recommends that guidance is included on this point. • Combination therapy, particularly with drugs from different classes, may potentially result in	

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	synergistic or additive antiviral activity, or prevent or delay the emergence of resistance. Specific guidance on the development of combination therapy should therefore be included. • The guidance should address the specific issues associated with the conduct of clinical trials in influenza in third countries that will be used for regulatory purposes in the EU (e.g., relevance of influenza strains, patterns of clinical illness, etc.).	
	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.	

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)*
		Comment: Proposed change (if any):	

Please add more rows if needed.