30 June 2015

Submission of comments on 'Concept paper on the need for revision of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials' (EMA/CHMP/QWP/126334/2015)

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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually. ACRO fully supports the stated aims of the Concept Paper on the need to update and revise the current guideline to be in line with the new EU Clinical Trial Regulation (No. 536/2014), and to give clearer guidance to Sponsors on quality data to be submitted, as well as a clearer reference to the	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	assessors in their evaluation work, thus facilitating a higher level of harmonisation among the EU Member States. The current guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004) covers chemically defined active substances, synthetic peptides, herbal substances, herbal preparations and chemically defined radio-active/radio-labelled substances. ACRO recommends that the Agency should similarly update the companion guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008) to ensure it is in line with Regulation 536/2014. A related companion document is the template for the Qualified Person's (QP) Declaration Equivalence to EU GMP for Investigational Medicinal Products Manufactured in Third Countries (ARTICLE 13(3)(b) OF DIRECTIVE 2001/20/EC). http://ec.europa.eu/health/files/eudralex/vol-10/2013-12_qp_template_imp.pdf	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	ACRO recommends that the QP Declaration template cross-reference the revised Quality Guideline and that links between the IMPD and the QP Declaration should be clarified in the Guideline, especially with respect to • the listing of manufacturing sites (substance and/or product) and • GMP Certification evidence harmonisation across CAs (i.e., for biological / biotechnological drug substances without an MA in the EU and manufactured in a third country). Confusion still exists as to whether the IMPD should contain the Non-clinical and Clinical information on the IMP, when the Investigator Brochure already covers this. In order to avoid having similar information contained in two documents (which are not always updated at the same time and may be reviewed by different assessors), ACRO recommends that the proposed guideline should specify the Non-Clinical and Clinical information should remain the remit of the Investigator Brochure, with the IMPD solely containing the Quality information. It should be made clear that the guideline does not address any requirements associated with manufacturing and/or import authorisations which will,	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	presumably, be addressed in separate legislation and/or guidelines.	

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)*
Lines 38 – 48		Comment: ACRO agrees that the revisions/updates described in this section are appropriate. Additionally, for more clarity, specificity and details we recommend that the guideline should make clear the requirements for clinical trials in each of the different phases of clinical research subject to Regulation (EU) No. 536/2014: Phase I, Phase II, Phase III and low-intervention clinical trials, for the benefit of both applicant and reviewer.	
Line 40		Comment: The elements referenced in this section are very relevant, and ACRO agrees that clarification of the text in these sections would be very welcome. In addition to the reference to shelf-life extensions, clarification relating to acceptable grounds for shelf-life assignment on the basis of extrapolation of real-time and accelerated stability data would be welcomed. An example of text to justify extrapolation could be provided with case studies on how to assign IMP shelf life based on real time and accelerated stability data. Some member states already provide such examples on their websites. For sterile products, ACRO suggests including the recommendations provided in the guideline for biopharmaceuticals for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs, in order to demonstrate the efficacy of aseptic processing operations. This section of the draft concept paper does not address any requirement for differentiation between innovator investigational medicinal products and generic versions. When a comparison study with the originator product is	

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)*
		performed to analyze various parameters as part of the pharmaceutical development of a generic product, ACRO recommends that it would be helpful to include guidance on selecting the age of the samples of originator product to be considered equivalent to the generic (as marketed originator product will be exposed to different conditions from generic products under development). This is especially important for sensitive products like dry powder inhalers and will help in generating uniform data throughout the Generics industry.	
Lines 42 - 43		Comment: ACRO recommends that the proposed revised guideline should include a more comprehensive and detailed list of examples of changes that will warrant a substantial modification. Current guidance on changes that will require a substantial amendment is incomplete and remains open to differences of interpretation by both applicants and assessors.	
Line 48		Comment: "Auxiliary medicinal product" (line 48) is a new term introduced and defined in Regulation (EU) No. 536/2014 as a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. As such, we recommend that the planned guidance on auxiliary medicinal products should take account of existing guidance on non-investigational medicinal products (NIMPs) used in clinical trials. It should explain clearly the relationship between different categories of auxiliary medicinal products and those of NIMPs, and should define the documentation requirements for the different	

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)*
		categories of auxiliary medicinal products, including for unauthorised auxiliary medicinal products or modifications not covered by the marketing authorisation. Proposed change (if any): Documentation requirements should be included, similar to that which is currently included in the existing NIMP-IMP guidance Annex 2.	
Lines 54 - 57		Comment: ACRO notes and supports the proposal that scientific updates resulting from this revision are incorporated in the current guideline (CHMP/QWP/185401/2004) in order to accommodate the transitional period defined in Regulation (EU) No. 536/2014 (Article 98), in which clinical trials can be started either in line with the current Directive 2001/20/EC or the new Regulation (EU) No. 536/2014. Such updates to the current guideline, however, should not include requirements introduced by Regulation (EU) No. 536/2014 that are not included in Directive 2001/20/EC. Alternatively (and preferably), the guideline should be drafted in a manner that indicates which requirements apply, depending on whether the trial is operating under the regulation or under the directive, respectively. Proposed change (if any): The above alternative (second) option is preferred in order to ensure that Regulation (EU) No. 536/2014 specific requirements are also captured/specified prior to applying the regulation.	

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)*
Lines 58 - 63		Comment: The Proposed Timetable foresees that a draft of the updated guideline will be available 6 months after adoption of the Concept Paper (i.e., August 2015) and, following a 3 month consultation period, the guideline will be finalised after a further 3 months (i.e., February 2016) and come into operation 6 months after adoption (i.e., August 2016). While this timetable would work for the update of the current guideline to take account of scientific progress, it is not acceptable for the implementation of an updated guideline taking account of the legal requirements of Regulation (EU) No. 536/2014, which could come into effect on 28 May 2016. Proposed change (if any): The Proposed Timetable should be revised to ensure that the final updated guideline is adopted no later than December 2015 (i.e., 6 months before the potential implementation date of Regulation (EU) No. 536/2014).	
ACRO thanks the European Medicines Agency (EMA) for the opportunity to submit comments on the draft of the “Concept paper on the need for revision of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.” Please do not hesitate to contact us if we can provide additional information (knoonan@acrohealth.org or +1 202 464 9340).			

Please add more rows if needed.