19 November 2015

To: European Commission
DG Health and Food Safety
Unit D6 "Medicinal products – Quality, Safety and Efficacy"
B-1049 Brussels

From: ACRO (Association of Clinical Research Organizations)

RE: ACRO Comment/Response – "GL on GMP for IMP"
Consultation document -- Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014

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 is pleased to provide the following comments on the detailed guidelines.

Lines 98 – 111: ACRO welcomes and supports the transfer into the proposed guidelines of the clarification in the current Eudralex Volume 4, Annex 13 guideline ("current guidelines") that reconstitution, as defined in the guidance, is not a manufacturing process. This has been the subject of significant confusion in the past.

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Lines 116 – 120: ACRO is concerned that, while the guidelines state clearly that this is outside their scope, some issues concerning the manufacture of auxiliary medicinal products are addressed. It is ACRO's view that, as auxiliary medicinal products represent a new category of product defined by Regulation (EC) No. 536/2014, there is scope for considerable confusion with regard to requirements for auxiliary medicinal products. ACRO therefore recommends that a separate guidance document on the requirements for auxiliary medicinal products should be generated, and the current document should be limited to investigational medicinal products (IMPs).

Lines 132 – 139: ACRO concurs with the idea that the level of supervision of suppliers be proportionate to the risk.

Lines 207 - 235: ACRO notes that the draft guidelines include a requirement for a product specification file, when the accompanying consultation on the Commission Delegated Act specifically invites views on whether or not a requirement for a product specification file would be useful. The impression given is that, while noting that a requirement for a product specification file is included in the current Annex 13 of the EU Good Manufacturing Practice guidelines, a decision on this as a requirement under Regulation (EU) no. 534/2014 has already been reached prior to initiating the accompanying consultation. ACRO considers that, as in current guidelines, a product specification file can be helpful provided that the requirements for its content are proportionate to the development status of the investigational medicinal product (IMP), the phase of clinical study, the planned extent of human exposure in the clinical trial, the proposed duration of the clinical trial, the dosage form, and the amount of information otherwise available. Additionally, ACRO recommends that the product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability of the previous versions in accordance with good documentation practices, and that the product specification file should contain all the required documents as currently outlined in Annex 13.

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Line 270: Similarly, ACRO is concerned that the draft guidelines propose a 25 year retention period for batch documentation when this is again a subject on which the accompanying consultation on the Commission Delegated Act specifically invites views. In this case, ACRO does not support a retention period of 25 years. ACRO is not aware of any difficulty created by the current requirements for retention of batch documentation for investigational medicinal products detailed in Directive 2003/94/EC. ACRO therefore sees no reason for current requirements to be changed so recommends retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. The sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with the Annex I to Directive 2001/83/EC, if required for a subsequent marketing authorisation.

Line 289 - 290: This extends validation requirements from premises and equipment to the entire process, taking into account the stage of product development. ACRO recommends that it be clarified that this should mean that the extent of validation is proportionate to the stage of product development.

Line 340: This refers to comparability of expiry date and of clinical trial. ACRO proposes that the wording used is that used in current guidelines (i.e. compatibility) since this allows for the expiry date to exceed that of the trial end whereas comparable dates would require the same date for both expiry and trial end.

Lines 355 – 362: This section, dealing with re-labelling in cases where the expiry date of the IMP is changed, does not recognise that , frequently, IMPs that have already been supplied to investigational sites may be relabelled by site staff or clinical research monitors acting on behalf of the sponsor to show updated expiry dates. ACRO therefore recommends that the guidelines include the current text from Annex 13 of the EU Guidelines for Good Manufacturing Practice: *This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.* This should also be reflected in the requirements for QP release (see Lines 485 - 486).

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Line 377: ACRO welcomes and supports the requirement that verification of the effectiveness of blinding should be performed and recorded.

Line 378 – 423: Compared to current guidelines, the storage period for reference and retention samples has been omitted i.e. at least 2 years after completion or formal discontinuation of last trial in which the batch was used, whichever is longer. Also omitted is consideration that retention samples be stored until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results. ACRO recommends that this text be included in order to limit the period for which storage is required.

Lines 382 – 387: ACRO recommends that the first sentence in the definition of a Reference sample should end with "…….should the need arise, during the shelf life of the batch concerned." It is ACRO's view that the scientific value of any re-analysis performed beyond the shelf life of the batch may be questionable.

Lines 392 – 400: Retention samples are primarily used in cases where the authenticity of a product needs to be confirmed (e.g. counterfeit identification). Where reference samples and retention samples are inter- changeable, are sufficient in quantity and presented identically, there should be no requirement for retention samples. Availability of printed materials (literally or in the form of an electronic file or (as newly proposed) photograph) should be accepted without the need for retention samples. As retention samples are typically trial specific and stored only for purposes of confirming visual identity, ACRO supports the use of an electronic file or photograph of the IMP, packaging and labelling in place of a formal Retention sample. However, ACRO is concerned that the draft guidelines include this proposal at the present time when this is again a subject on which the accompanying consultation on the Commission Delegated Act specifically invites views. Again, the impression given is that a decision on this has been reached prior to initiating the accompanying consultation.

Lines 485 - 486: As outlined under Lines 355 – 362, ACRO proposes that this be rephrased in line with current guidelines i.e. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question.

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Line 505: The current guidelines state that "The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied." ACRO suggests that this text be retained as it provides a mechanism for communicating comparator recalls.

Line 513: The current guidelines state that "Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures." ACRO proposes that this text be retained as it ensures understanding by all parties of roles and responsibilities.

Line 532: Clarification regarding the definition "Preparation" is proposed as the only reference to preparing within the guidelines relates to preparation of documents. The processes described under preparation constitute packaging and labelling and, as such, it is unclear why a separate definition is required. While definitions of shipping, transport and distribution are included, the guidelines do not address these topics. ACRO recommends that text from the current guidelines be included in the proposed guidelines.

Thank you for this comment opportunity. Should you have any questions or require further information, please do not hesitate to contact ACRO at knoonan@acrohealth.org.

Respectfully submitted,

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