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)

ACRO Comment on Public Consultation: "DA on GMP for IMP"
European Commission’s consultation document on a Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures, pursuant to the first 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 thanks the Commission for the opportunity to provide these comments.

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ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

I. ACRO responses to specific questions in the consultation document

Question 1a: Would a requirement for a product specification file (a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product) be useful to be introduced?

ACRO notes that current guidance in Annex 13 of the EU Good Manufacturing Practice guidelines includes a requirement for a product specification file as do the proposed Commission guidelines on good manufacturing practice for investigational medicinal products for human use. It is therefore assumed that the proposal in the context of the above question is to introduce this requirement into legislation, via the delegated act. ACRO considers that 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 considers 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 practises, and should contain all the required documents as outlined in the current Annex 13. Such flexibility should be referenced specifically in the proposed legislation and be consistent with current practice.

Question 1b: Do product specification files exist for manufacture of all investigational medicinal products in the EU?

The experience of ACRO member companies is that product specification files do exist for investigational medicinal products used in clinical trials in the EU, but ACRO does not have the information needed to confirm whether product specification files exist for all investigational medicinal products in the EU.

Question 2: Different options exist for the retention period of batch documentation:
a) Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period.
b) Retention for at least 25 years after the end of the clinical trial in line with the retention period of the clinical trial master file.
Please indicate the preferred option with justification.

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 and so recommends that the current text of the Directive is incorporated into the planned Delegated Act, as follows: *For an investigational medicinal product, the batch documentation shall be retained 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.* ACRO also recommends that the requirements should apply equally to all forms of document media types.

Question 3: Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please elaborate your answer to this question.
ACRO does not agree that this would be not always practical in all cases, and also queries why this would be considered necessary. Investigational medicinal products from a single batch may be split into several shipments by a manufacturer outside the European Union for delivery into the EU. Each shipment, since it comprises the same batch, would be covered by the same certificate of analysis. While ACRO considers it is important that the EU importer is provided with a copy of this certificate, for the reasons stated in the question, the value of providing a duplicate copy of the certificate with each shipment is not clear. However, the major difficulty occurs in the case of active comparators (which may be considered investigational medicinal products under Regulation 536/2014), when certificates of analysis are not always available to the sponsor of the trial, particularly in the case of commercially available products. It is ACRO's view that, if the product is sourced regionally, reference to its marketing authorisation should suffice. However, if it is not sourced regionally, manufacturer's site registration, product registration or Certificate of Analysis (CoA)/Certificate of Conformance (COC) are normally requested. Where not available, a pedigree statement or a statement of authenticity is normally requested. It would therefore constitute an unnecessary administrative burden.

Question 4a: Should retention samples also be required to be retained by the manufacturer?

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 photograph) should be accepted without the need for retention samples.

Question 4b: If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify.

Please see above response to question 4a.

Question 5a: In how many clinical trials authorised under the Clinical Trials Directive has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

ACRO does not have the information needed to answer this question.

Question 5b: In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorised in an ICH country (EU, US, Japan, Canada and Switzerland)? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available.

ACRO does not have the information needed to answer this question.

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II. Additional ACRO comments on the text of the consultation document

Line 91: This states that “personnel shall receive internal and on-going training”. It is assumed that this is intended to state “personnel shall receive initial and on-going training”.

Lines 62-64: The statement “The importer of investigational medicinal products for human use shall ensure that the manufacturer located in a third country is entitled to manufacture the relevant type of investigational medicinal product in that country” is a request to demonstrate in-country regulatory compliance rather than GMP equivalency with EU GMP. In cases where no Manufacturer's Authorisation or GMP Certificate is issued by a third country regulatory authority for a manufacturer in that country further clarification is required regarding the expected documented evidence to support the requirement "The importer of investigational medicinal products for human use shall ensure that the manufacturer located in a third country is entitled to manufacture the relevant type of investigational medicinal product in that country." ACRO proposes use of the term "not prohibited from" instead of "entitled to" to allow for global country specific regulatory variances in this context.

Lines 172 – 173: ACRO welcomes and supports the clear statement that “When products are imported from third countries, analytical control in the Union shall not be mandatory.” Additionally, ACRO recommends adding the statement "Where they are manufactured in conditions at least equivalent to EU standards of Good Manufacturing Practice."

Line 179, 186, 195: Compared to the GMP Directive, ACRO notes that the responsibility for final control as well as for unblinding procedures shifts from the sponsor to the manufacturer and clarifies that sample retention is the responsibility of the manufacturer. These clarifications are welcomed.

Lines 184 – 188: ACRO is concerned by the statement that "Sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished investigational medicinal product batch shall be retained by the manufacturer for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer." While this is currently required under Commission Directive 2003/94/EC (8 October 2003) laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, in the case of Reference samples, it is ACRO's view that the scientific value of any re-analysis performed beyond the shelf life of the batch may be questionable and, in the case of Retention samples, as noted in the response to question 4 above, ACRO considers that retention samples should not be required. As retention samples are typically trial specific and stored only for purposes of confirming visual identity, ACRO recommends that this can be accomplished by means of an electronic file or photograph of the IMP, packaging and labelling. With regard to reference samples, ACRO proposes that they should be retained by the manufacturer for at least one year after the shelf-life of drug product or at least two years after discontinuation/completion of the Clinical Trial, whichever is the longest.

Lines 204 – 218: This section of the document describes the responsibilities of the qualified person, but the qualifications and experience that will be required of a qualified person under the Delegated Act are not described in the document. Current legislation allows for a person who was carrying out the duties of a qualified person prior to the introduction of Directive 2003/94 but who did not have the relevant qualifications to continue in this role as a "transitional qualified person". Transitional qualified persons have extensive experience of the issues associated with good manufacturing practice and batch release of investigational medicinal products, and many are still employed in this role. ACRO therefore considers it is important that the Delegated Act should allow for transitional qualified persons recognised under current legislation to continue in the role.

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Lines 263 – 265: ACRO recommends that the statement "Where required by the protocol of a clinical trial, the manufacturer shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall" is clarified. ACRO believes that the statement means that a procedure for rapid unblinding is not required in trials where blinding is not required by the protocol. However, the statement could be interpreted as meaning that, even in blinded trials, a procedure for rapid unblinding will only be required if specified in the protocol. ACRO does not consider this would adequately protect trial subjects and is of the view that, in the interests of subject safety, a procedure for rapid unblinding should be in place and specified in the protocol for all double-blind trials.
ACRO also considers that this statement does not satisfactorily reflect the responsibility of the clinical trial sponsor with regard to unblinding and recommends that this is made clear. Responsibility for ensuring that all aspects of the clinical trial comply with the relevant regulatory requirements lies with the sponsor, who is therefore responsible for ensuring that a procedure for the rapid unblinding of blinded products is in place where this is necessary for a prompt recall. The role of the manufacturer is to follow the procedure, when required.

Lines 292 – 293: In relation to GMP inspection of IMP manufacturers outside the EU, these lines state "The frequency of such inspections shall be based on an assessment of risk". While ACRO fully supports a risk-based approach to inspection as the most effective use of available inspectorate resources, the reference to frequency implies that a non-EU IMP manufacturing site will be subject to repeat inspections. ACRO does not believe that this has been the approach previously (except in exceptional circumstances to confirm that significant findings identified in a previous inspection have been corrected) and is concerned that there is insufficient GMP inspectorate resource available in the EU to commit to repeated inspection of non-EU IMP manufacturing sites. It is the responsibility of manufacturing authorisation (including those specific to IMP importation) holders in the EU to verify that the third country manufacturer operates in accordance with GMP standards at least equivalent to those laid down in the Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products and on inspection procedures and the Commission guidelines on good manufacturing practice for investigational medicinal products for human use. Consequently, ACRO suggests amending the proposed statement to "Such inspections shall be based on an assessment of risk." Moreover, ACRO proposes that the criteria for any risk based approach be shared, in the interests of transparency.

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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