15 December 2016

Submission of comments on Draft guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1)

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 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 welcomes and supports the draft guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trial. However, ACRO believes that it could be strengthened by closer alignment with the equivalent guidance (currently in revised draft form) on the requirements to the chemical and pharmaceutical quality	

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	documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015). In particular, ACRO recommends that greater emphasis is given to the following principles: • Adoption of a risk-based approach to documentation requirements focused on risk aspects of the investigational medicinal product, taking into account not only the nature of the product and the state of development/clinical phase, but also the patient population, nature and severity of the indication and the characteristics of the proposed clinical trial. • An emphasis on presentation of data in the form of succinct tabulated summaries, accompanied by an evaluation and justification, where appropriate, rather than a detailed description of studies and results. A related companion document is the template for the Qualified Person's (QP) Declaration of 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 ACRO recommends that the QP Declaration template cross-reference the revised Quality Guideline and that	

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	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 competent authorities (i.e., for biological / biotechnological drug substances without an MA in the EU and manufactured in a third country). Additionally, ACRO recommends that it should be made clear that the guideline does not address any requirements associated with manufacturing and/or import authorisations which will, 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)*
54 - 56		Comment: Regulation (EU) No. 536/2014 came into force on 20 June 2014 but, as currently estimated by the EMA, will not take effect until October 2018. The guideline should therefore clarify whether it will be effective only from the effective date of the Regulation or will be introduced earlier under current legislation (Directive 2001/20/EC). Proposed change (if any): Clarify whether the guideline will be effective only from the effective date of the Regulation or will be introduced earlier under current legislation (Directive 2001/20/EC).	
103 - 105		Comment: 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. Proposed change (if any): Add a statement to confirm that the Non-Clinical and Clinical information should remain the remit	

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		of the Investigator Brochure, with the IMPD solely containing the Quality information.	
139		Comment: Use of the word “adequately” in the sentence “The manufacturing process and process controls should be adequately described” is not helpful to clinical trial applicants. The guideline should state clearly what information will be considered adequate. If this is the information described in lines 140 – 154, this should be clearly stated. Proposed change (if any): State clearly what information will be considered adequate.	
149 - 150		Comment: ACRO recommends that a clear distinction should be made between development batches and clinical batches and any differences in manufacturing should be discussed. Proposed change (if any): Revise the statement to read “Batch(es) and scale should be defined, including information on any pooling of harvests or intermediates. A clear distinction should be made between development batches and clinical batches and any differences in manufacturing should be discussed.”	
177		Comment: The sentence “Information on the generation, qualification and storage of the cell banks is required” should be clarified as proposed below in order to avoid ambiguity.	

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		Proposed change (if any): Reword the sentence to read “The following information on the generation, qualification and storage of the cell banks is required.”	
191		Comment: The sentence “Any available data on cell substrate stability should be provided” implies that such data will never be a mandatory requirement for trial approval. If this is so, it should be stated clearly or the circumstances in which cell substrate stability will be required should be described. Proposed change: Make clear that cell substrate stability data should be submitted if available, but are not mandatory (except in certain circumstances that should be described in the guideline).	
197 - 199		Comment: ACRO concurs that, with the noted exception of manufacturing steps to remove or inactivate viral contaminants, information on process validation and/or evaluation is not applicable for a risk assessment of active substances intended for clinical trial use, and welcomes this recognition. Proposed change (if any):	
210 - 211		Comment: ACRO recommends that the proposed justification should be based on a risk-based assessment.	

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		Proposed change (if any): Revise the statement to read "If process changes are made to steps involved in viral clearance, a risk-based justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable."	
213 - 215		Comment: ACRO recommends clarifying that the comparability exercise should follow risk-based principles, using pre-defined criteria to establish comparability. Proposed change (if any): Revise the statement to read: "Depending on the consequences of the change introduced and the stage of development, a risk-based comparability exercise may be necessary to demonstrate that the change would not adversely impact the quality of the active substance. The comparability exercise should be based on pre-defined criteria."	
234 - 235		Comment: Use of the word "adequate" in the sentence "Adequate characterisation should be performed in the development phase prior to phase I and, where necessary, following significant process changes" is not helpful to clinical trial applicants. The guideline should state clearly what information will be considered adequate. If this is the information described in lines 236 - 242, this should be clearly stated.	

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		Proposed change (if any): State clearly what information will be considered adequate.	
253 - 255		Comment: The sentence “When process validation data are incomplete, the quality attributes used to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes” is confusing relative to the statement in lines 197 – 199 that process validation data are not required to be submitted. Process validation data that exist but are not submitted will not be known to the reviewing competent authorities, who, as a result, may wrongly consider the quality attributes used to control the active substance to be inadequate. Proposed change (if any): The guideline should describe how clinical trial applicants should explain the use of quality attributes to control the active substance in the absence of submitted process validation data.	
255 - 257		Comment: ACRO recommends that quality attributes not included in the specification should be pre-defined and justified. Proposed change (if any): The statement should be revised to read: “Therefore the quality attributes controlled throughout	

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		the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set. Quality attributes not included in the specification should be pre-defined and justified."	
265 - 267		Comment: ACRO recommends that any differences in the manufacturing process between development batches, clinical batches and non-clinical batches should be summarized and explained. Proposed change (if any): Revise the statement to read: "As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development. Any differences in the manufacturing process between development batches, clinical batches and non-clinical batches should be summarized and explained."	
280 - 281		Comment: ACRO considers that it is important for evaluation purposes that the controls used in non-compendial analytical procedures are presented. Proposed change (if any): Revise the statement to read " A brief description of all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided, highlighting controls used in the analysis."	

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309 - 310		Comment: ACRO recommends that any manufacturing process differences between batches should also be identified. Proposed change (if any): Revise the statement to read: “The manufacturing process used for each batch and any differences in these processes should be identified.”	
314 - 326		Comment: As above (comment on lines 253 – 255). Proposed change (if any): The guideline should describe how clinical trial applicants should explain the use of quality attributes in the specification and acceptance criteria to control the active substance in the absence of submitted process validation data.	
331 - 333		Comment: Use of the words “adequate” and “adequately” in the sentence “The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be adequately described” is not helpful to clinical trial applicants. The guideline should state clearly what information will be considered adequate. Proposed change (if any): State clearly what information will be considered adequate.	
345 - 346		Comment: ACRO recommends that more guidance should be	

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		provided here as some Member State regulatory authorities accept a general description of the container/closure system whereas others routinely ask for sponsors to confirm that the components of the container/closure system comply with applicable Ph.Eur monographs, EC Directives and EC Regulations. For example, recent examples of questions received by ACRO member companies during evaluation of clinical trial applications are: - "It should be confirmed that the plastic manufactured by XXXX meets Regulation (EC) 10/2011 and its amendments." - "The Applicant should confirm that the drug substance is packaged in a container closure system that meets the corresponding relevant standards in force (i. e. Directives, Eur. Ph. etc.)." Proposed change (if any): Clarify in more detail the level of information required on the container/closure system.	
428 - 429		Comment: ACRO recommends clarifying that the comparability exercise should follow risk-based principles, using pre-defined criteria to establish comparability. Proposed change (if any): Revise the statement to read: "An appropriate comparability exercise with supporting risk-based assessment should support significant changes, e.g. formulation changes."	

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476 - 478		Comment: ACRO recommends that consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture. Proposed change (if any): Revise the statement to read: “References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. For excipients not covered by any of the aforementioned standards, an in-house specification should be provided. Consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture.”	
483		Comment: ACRO concurs that validation data on the analytical procedures applied to the excipients are not required in a clinical trial application, and welcomes this recognition. Proposed change (if any):	
485		Comment: ACRO recommends that consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture. Proposed change (if any): Revise the statement to read: “For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified. Consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture.”	

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539 - 540		Comment: ACRO recommends that any manufacturing process differences between batches should also be identified. Proposed change (if any): Revise the statement to read: “The manufacturing process used for each batch and any differences in these processes should be identified.”	
622 - 650		Comment: ACRO recommends that the final guideline should include a more comprehensive and detailed list of examples of changes that will warrant a substantial modification, and also a cross-reference to the examples given in the guideline on requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015). Experience shows that the question of whether a change is sufficiently significant to require a substantial modification of the clinical trial approval remains open to differences of interpretation by both applicants and assessors. Consequently, the guidance should be as comprehensive as possible on this topic. Proposed change (if any): Include a more comprehensive and detailed list of examples of changes that will warrant a substantial modification.	
622 - 650		Comment: Additionally, there is a specific need to include guidance on the commonly encountered situation where there	

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		is a change in material of the container used for administration of the IMP, e.g. in the case of a concentrate for solution for infusion that is diluted prior to infusion and administered via infusion from a saline bag, does the change to an infusion bag manufactured from a different type of plastic (e.g., polyolefin instead of PVC) warrant a substantial modification? Proposed change (if any): Clarify whether a change of material for an infusion bag would constitute a substantial modification.	
Missing issue		Comment: For IMPs that are proposed biosimilars, it would be helpful if the document included guidance on where the biosimilarity exercise information should be provided within the IMPD. In the absence of current guidance, the experience of ACRO member companies is that a number of sponsors have included a Regional section at the end of the IMPD, after the appendices. This has been accepted by national competent authorities, but clear guidance from the EMA would be welcomed by sponsors and CROs. Proposed change (if any): Include guidance on where the biosimilarity exercise information should be provided within the IMPD. ACRO thanks the Agency for this opportunity to provide	

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		comment on Draft guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1). Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide any additional information or answer any questions.	

Please add more rows if needed.