30 August 2021

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. 2 corrigendum)

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 clinical research and technology organizations. Our fourteen member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support the majority of all biopharmaceutical sponsored clinical investigations worldwide. With more than 200,000 employees, including over 60,000 in Europe, engaged in research activities in 114 countries the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO welcomes the opportunity to comment on the draft revision of the European Medicines Agency (EMA) guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. We welcome the flexibility shown in the individual sections of the guideline that permit a risk-proportionate approach to be taken to specific data and documentation	

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	requirements. However, we recommend that the guideline would benefit from a clear statement on this in the Introduction, which could be similar to that used in the equivalent guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/31884/2021): "It should be clearly differentiated between the requirements for a dossier for a clinical trial and a marketing authorisation dossier. Whilst the latter ones have to ensure a state-of-the-art quality of a product for wide use in patients, information to be provided for investigational medicinal products (IMPs) should focus on the risk aspects and should consider the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself. As a consequence, it will not be possible to define very detailed requirements applicable to all sorts of different products. However, guidance on standard information which should normally be presented in the quality part of an IMPD is provided in this guideline." Our specific comments on the text of the draft guideline are as follows:	

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)*
291 and 541		Comment: For clarity, we recommend adding the sentence below at the end of each paragraph. Proposed change (if any): Add "Any changes made should be described and justified."	
295-296		Comment: We recommend for consistency and clarity that a statement is added similar to that used in section 1.5 of the equivalent guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/31884/2021), i.e. "When compiling the documentation, the difference between "analytical procedure" and "analytical method" should be kept in mind. The term "analytical procedure" is defined in ICH Q 2 (A) and refers to the way of performing the analysis. The term "analytical method" refers to the principles of the method used." Proposed change (if any): Add the statement recommended above.	
650		Comment: The guideline reference should be updated to EMA/CHMP/QWP/31884/2021.	

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		Proposed change (if any): Update the reference.	
728		Comment: The draft guideline currently states that "Addition or replacement of importation, QP release or QC testing Sites" will be considered a substantial modification. However, during the COVID-19 pandemic, the European Commission, the EMA and the Heads of Medicines Agencies (HMA) agreed on a series of measures to mitigate the impact of disruptions caused by COVID-19. Question 2.5 in the Questions and Answers document on regulatory expectations for medicinal products for human use during the Covid-19 pandemic (Revision 3, 1 July 2020) notes that "remote batch certification is permissible under EU GMP rules, provided that the QP has access to all information necessary to enable them to certify the batch." In the absence of any issues associated with remote QP certification during the pandemic, we therefore recommend, in order to provide flexibility and improved efficiency, that remote QP certification is included as a permissible alternative to stating the site of QP certification, both in initial clinical trial applications and as a later substantial modification. Proposed change (if any): Include the possibility for remote QP certification.	

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694 - 703		Comment: The guideline should explain that the non-substantial changes under Art 81.9 will still be considered non-substantial and may be implemented without prior notice in CTIS. In CTIS an Art 81. 9 non-substantial modification submission pathway is prevented, when there is an ongoing application under evaluation affecting the same dossier part. Thus, it is important to note, that such changes may still be implemented, while their notice in CTIS may be delayed until the ongoing application evaluation is decided and the CTIS is free again. Proposed change: Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are concept introduced under the CTR, which aims to update certain, specified information in the CTIS via the non-substantial modification submission pathway without the need for an substantial modification application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Since those Art 81.9 changes are non-substantial they may be implemented prior to their submission in CTIS via the non-substantial modification submission pathway. Art 81.9 states "The sponsor shall permanently update in the EU database information on any changes to the clinical trial which are not	

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		substantial modifications but are relevant for the supervision of the clinical trial by the Member states concerned".	
720		Comment: Suggest to align examples and verbiage between both guidelines for consistency reasons Line 1267: examples/verbiage *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and Line 720: examples/verbiage *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"*	
727		Suggest to align examples and verbiage between both guidelines for consistency reasons Line 1272: examples/verbiage *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and Line 727: examples/verbiage *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"*	
728		Suggest to align examples and verbiage between both guidelines for consistency reasons Line 1273: examples/verbiage *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and Line 728: examples/verbiage *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"*	
735		Comment: Shelf-life stability plans/protocols/scheme could be submitted and approved not only during initial	

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		application, but also via subsequent substantial modifications. Thus, the currently approved plan/protocol/scheme should apply. Suggest to also align verbiage between both guidelines for consistency reasons with line item 1282 *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and corresponding line item 735 *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"* Proposed change: Include to clarity reasons Extension in Shelf-Life period based on the currently approved shelf-life stability protocol or scheme.	
		ACRO thanks the Agency for the opportunity to provide these comments. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can answer any questions or provide additional details.	

Please add more rows if needed.