EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2021

Submission of comments on Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/31884/2021)

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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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 to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. We welcome the flexibility shown by the EMA in recognising that information to be provided for investigational medicinal products (IMPs) should focus	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	on the risk aspects and take into account 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. 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)*
288		Comment: Given the context of the preceding sentence, we assume that the statement "For organic-chemical precursors, the same information should be provided as for drug substances" applies only to radionuclide products, but this is not clear from the statement. Proposed change (if any): Clarify the statement as noted above.	
397-398		Comment: The "relevant guidelines" considered appropriate by the EMA should be referenced. Proposed change (if any): Include appropriate references.	
523, 761, 975 and 1275		Comment: 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	

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)*
		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. Proposed change (if any): Include the possibility for remote QP certification.	
724		Comment: The document should clarify what is meant by "ICH regions", i.e. whether this includes territories whose regulatory authorities are observers in the ICH process or includes only full members of ICH. Proposed change: Clarify as noted above.	
1236		Comment: Typographical error. Proposed change: "are concept" should read "are a concept".	
1238, 1243 and 1245		Comment: Typographical error. Proposed change: "an" in each of these lines should read "a".	

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)*
1265		Comment: We recommend adding the sentence below at the end of the paragraph. Proposed change: Add the following sentence: "In case of doubt, the sponsor should consult the Reporting Member State."	
1236 - 1245		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	

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)*
		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 substantial modifications but are relevant for the supervision of the clinical trial by the Member states concerned".	
1267		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"*	
1271		Comment: Should explain, that a retest scheme is not limited to be submitted with the initial application, but could also be later submitted and approved via a substantial modification. Suggest to also align verbiage between both guidelines for consistency reasons *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"*	

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)*
		Proposed change: Extension of retest period based on the currently approved shelf-life stability protocol or scheme Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if: • each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol • the extension is covered and in compliance with the approved stability protocol • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature	
1272		Comment: 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"*	
1273		Comment: Suggest to align examples and verbiage between both guidelines for consistency reasons Line 1273: examples/verbiage *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and	

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)*
		Line 728: examples/verbiage *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"*	
1280		Comment: Suggest to also align verbiage between both guidelines for consistency reasons *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and *"guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"* Proposed change: Replace "container" by "immediate package" Include under non-substantial change the example from the biological guideline: • Changes to secondary packaging • Change of supplier (deletion, replacement or addition) of packaging components if the material is identical and specifications are at least equivalent.	
1282		Comment: Shelf-life stability plans/protocols/scheme could be submitted and approved not only during initial 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 *"guideline-requirements-chemical-pharmaceutical-quality-documentation"* and corresponding line item 735 *"guideline-requirements-quality-*	

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)*

		documentation-concerning-biological-investigational-medicinal"
		
		Proposed change:
		• Reduction in Shelf-Life if not safety or quality related
		• Extension in Shelf-Life period based on the currently approved shelf-life stability protocol or scheme. Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if:
		  • each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol
		  • the extension is covered and in compliance with the approved stability protocol
		  • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature	

		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.