EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/CHMP/BWP/518880/2021
Committee for medicinal products for human use (CHMP)

Overview of comments received on the draft Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 Rev. 2)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1.	EFPIA
2.	AstraZeneca Pharmaceuticals
3.	Takeda
4.	ACRO (Association of Clinical Research Organizations)
5.	Regeneron Pharmaceuticals, Inc.

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1.	Please see general comments regarding Art 81.9 notifications for CMC changes included in Chemical and Pharmaceutical Guideline comments. It is also noted that there are inconsistencies between the two Guidelines, but the Biologicals Guidance should be considered as the template.	Noted. Relevant comments have been considered when preparing the final version.
1.	The revision to the IMPD guidance for modifications to the quality component of the IMPD is restricted to post-approval changes and does not provide the opportunity to adopt a more science and risk-based approach to biologics that modernises the overall guidance to the current level of understanding for biologics and the industries current understanding of the manufacture and control of biologics. This would provide a more streamlined transition from the clinical IMPD to the commercial MA and alignment with more recent ICH approach to commercial regulatory expectations. Furthermore, a greater risk-based approach to changes could improve supply and reduce product development timelines, thereby getting medicines to patients faster.	Noted. This consultation was limited to revision of chapter 6.
1.	In the Clinical Trial Regulation CTR No 536/2014, Article 81.9 mostly refers to the maintenance of the information in the EU database and requires that information relevant for the supervision of the clinical trial are kept up to date. It is perceived that the current content of the guideline does not give enough information for sponsors to clearly understand which type of CMC information is understood as relevant for the supervision of the trial. Further examples and principles would be helpful.	Noted. Relevant comments have been considered when preparing the final version.

Stakeholder no.	General comment	Outcome (if applicable)
1.	If the INN or trade name is issued during ongoing clinical study, what is the timeframe within the sponsor should update the EU database (CTIS) to provide this information as non-substantial modification?	This issue is not subject of the quality guideline. The requirement to notify a change of name or code of the active substance or IMP via Art 81.9 NSM has been deleted from the final version.
1.	If the sponsor decides to change the label content with INN name, does the sponsor need to provide a description of the changed content of the labelling at next substantial amendment?	This issue is not subject of the quality guideline. Currently regulated via CT-1 guideline. The requirement to notify a change of name or code of the active substance or IMP via Art 81.9 NSM has been deleted from the final version.
1.	More detail would be helpful re what information is expected to be provided for auxiliary medicinal products (AxMPs), since AxMPs are only mentioned in sections 1.2 and 6 (the latter is a new inclusion).	Noted. This consultation was limited to revision of chapter 6.
3.	The opportunity to review the guidance for biologic IMP information alongside the general guidance for requirements to the chemical and pharmaceutical quality documentation (EMA/CHMP/QWP/31884/2021) is welcome. The exercise highlights discrepancies between the two guidelines. Several parts of the table in section 6 could benefit from alignment with the table in section 9 of the general guidance. Based on statements within this guidance there is generally no reason to require a higher level of scrutiny for changes to IMPs for biologics than for changes to non-biologics, on the basis of increased risk to patients, but the classifications of changes continue to require increased levels of reporting for biologics. In addition, the revision of this guideline should include the change to "drug substance" from "active substance" to align with ICH terminology.	Noted. Relevant comments have been considered when preparing the final version.

Stakeholder no.	General comment	Outcome (if applicable)
4.	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 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	Noted.

Stakeholder no.	General comment	Outcome (if applicable)
	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:	
5.	Regeneron welcomes the initiative by the Agency in proposing this revised guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.	Noted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
123	3.	Comment: The revision should include the change to "drug substance" from "active substance" to align with ICH terminology Proposed change (if any): S ~~Active~~ Drug Substance	Not accepted. This consultation was limited to revision of chapter 6.
165	1.	Comment/Rationale: There is no discussion on Master or Working Virus Seed. Please include unless viral vaccines are not in scope of this guidance. Please clarify in the scope section accordingly.	Not accepted. This consultation was limited to revision of chapter 6.
167-170	1.	Comment/Rationale: Please clarify whether reference to quality standards (e.g., compendial monographs or manufacturers' in-house specifications) is necessary for materials such as column resins or microcarrier beads which are not consumed by the process.	Not accepted. This consultation was limited to revision of chapter 6.
276	1.	Comment/Rationale: Quantitative acceptance criteria for quantity are not appropriate for drug substance. The quantity needs only to be high enough to meet the needs to formulate the drug product. 'Report results' is acceptable to begin understanding of yield process capabilities. Proposed change: Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a limit of 'record' or 'report results' will not be acceptable for these quality attributes, with the exception of quantity.	Not accepted. This consultation was limited to revision of chapter 6.
291 and 541	4.	Comment: For clarity, we recommend adding the sentence below at the end of each paragraph.	Not accepted. This consultation was limited to revision of chapter 6.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Add "Any changes made should be described and justified."	
295-296	4.	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.	Not accepted. This consultation was limited to targeted revision of chapter 6.
331	1.	Comment/Rationale: The chapter S.4.4 gives details but does not mention CoAs. Proposed addition: "Certificates of Analysis are not required."	Not accepted. This consultation was limited to targeted revision of chapter 6.
458-460	1.	Comment/Rationale: The details to be provided for the manufacturer(s) differ between this guideline and the one for chemical-pharmaceutical medicinal products. Proposed change: Align the two guidelines	Not accepted. This consultation was limited to targeted revision of chapter 6.
501-502	1.	Comment/Rationale:	Not accepted. This consultation was limited to targeted revision of chapter 6.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please clarify if there are expectations to validate analytical procedures for non-compendial excipients when the analytical method is not compendial.	
535	1.	Comment/Rationale: Please provide guidance on the acceptability of performing impurity testing on the drug substance and applying a specification to the drug product by calculation. For example, testing DS for endotoxin and calculating the expected endotoxin level in the DP based on dilution factor, to compare against a DP specification.	Not accepted. This consultation was limited to targeted revision of chapter 6.
562	1.	Comment/Rationale: The chapter P.5.4 gives details but is not mentioning CoAs. Proposed addition (see also line 331): "Certificates of Analysis are not required."	Not accepted. This consultation was limited to targeted revision of chapter 6.
579	1.	Comment/Rationale: Further clarification would be beneficial. Proposed change: For a non-integral drug-device combination product, in the absence of a CE mark for the intended purpose, a statement of compliance with the relevant essential requirements for medical devices with regards to safety and performance related device features is required.	Partly accepted. The text relating to medical devices (chapter 2, section P.7) has been updated with reference to the Medical Device Regulation.
582	1.	Comment/Rationale: Shouldn't it read "Medical Device Regulation" instead of "Medical Device Directive"?	Partly accepted. The text relating to medical devices (chapter 2, section P.7) has been updated with reference to the Medical Device Regulation.
624-626	1.	Comment/Rationale: Requirements for "Solvents for reconstitution and diluents" and "Placebo" are stated differently but for biologics they are normally interchangeable and therefore the requirements should be the same.	Not accepted. This consultation was limited to targeted revision of chapter 6.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (row 625, 626): "Information on the solvents to be provided in the IMPD should meet the requirements similar to placebo as outlined in section 6 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015)."	
632, 635	3.	Comment: This reference should be updated to the new number for this guidance (EMA/CHMP/QWP/31884/2021) Proposed change (if any): trials (EMA/CHMP/QWP/31884/2021).	Not accepted. The original document reference number is correct.
650	4.	Comment: The guideline reference should be updated to EMA/CHMP/QWP/31884/2021. Proposed change (if any): Update the reference.	Not accepted. The original document reference number is correct.
651-653	1.	Comment/Rationale: Please make sure that chapter 9 is in line with the corresponding guidelines on small molecules Proposed change: Harmonise the two guidelines	Accepted. The drafting groups have collaborated and harmonised the content of both guidelines as far as possible.
654-656	1.	Comment/Rationale: Auxiliary medicinal products usually are authorised Medicinal Products. Art. 65 of CTR requires the GMP manufacturing requirements (article 63.1 of same CTR) as for IMPs only for those Auxiliary medicinal products that are not authorised. Proposed change:	Not accepted. Proportional traceability and documentation requirements apply to all auxiliary medicinal products, regardless of whether authorised or unauthorised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP/unauthorised auxiliary medicinal product at the respective site …"	
685	1.	Comment/Rationale: Further clarification regarding the difference between what stands for a change relevant according to 81.9 and for a non-substantial modification would be appreciated. Additional clarification on what procedure corresponds to Art. 81.9 would be helpful such as "tell and do procedure" or "notification". Header of table indicates Art.81.9 change to be non-substantial modifications (NSM); proposal to add this classification in line 685 for clarity/consistency Proposed change: a non-substantial modification ~~change~~ relevant to the supervision of the trial (NSM Art. 81.9);	Not accepted. The wording in the guideline is according to CTR. Art 81.9. CTR EU (no) 536/2014: The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.
689	1.	Comment/Rationale: What is meant by "rights of the subjects" and how does a change impact this? Is it for example if there was a change to an excipient that could impact the subject because they have a pre-existing condition, e.g., an allergy? Proposed change: Clarification should be provided	See CTR Art. 2 (2) 13 Wording taken form the CTR 536/2014.
692 -693	3.	Comment: The reference to toxic degradation products is not relevant to biological IMPs, as noted in section 1.1 (line 74). The language in this section has been taken directly from the general guidance and should be corrected. The reference to TSE risk should be clarified instead. Proposed change (if any):	Partly accepted. Guideline wording updated:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		changes in impurities profile, microbial contamination, viral safety or changes in the risk of TSE contamination ~~and in some particular cases to stability when toxic degradation products may be generated~~.	or the risk of TSE contamination or in some particular cases to stability when degradation products of concern may be generated.
694	3.	Comment: Typographical correction Proposed change (if any): … supervision of the trial (Art 81.9 change) are concepts	Accepted.
694-703	1.	Comment/Rationale: Further clarification whether and how a single change according to Art. 81.9 should be submitted. Does GMP documentation (e.g., GMP certificate, MIA) fall under "specified information in CTIS"? A concrete definition example for the specified information in CTIS should be provided for better clarity about which non-substantial modifications are relevant for the supervision of the trial. Clarification on what procedure corresponds to Art. 81.9 would be helpful such as "tell and do procedure" or "notification". Clarifications and additional guidelines are needed regarding the process and the type of information to be uploaded to the CTIS, for example, how the information will be provided within the online application form within CTIS database, and if updated IMPD documentation should be submitted in support of Art 81.9 changes if they are notified without cumulating them with a substantial IMPD modification. In the event of an inspection of the investigational clinical site or a manufacturing site by any EU country HA, please clarify whether the country HA inspector would access the non-public CTIS information on a specific investigational product, and whether the supporting	Not accepted. This level of information is not required in the guideline on IMPD quality data requirements, however, these comments have been highlighted for consideration in CTIS procedural and training documentation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		documentation of an Art 81.9 change be requested to be available at such site.	
694 - 703	4.	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) is a 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 substantial modifications but are relevant for the supervision of the clinical trial by the Member states concerned".	As above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
702/703	1.	Comment/Rationale: The statement "The combination of different Art 81.9 changes can cumulate into a change that needs to be submitted as a substantial modification." is not clear. It is unclear how/why multiple changes relevant for trial oversight but not for patient´s safety can become relevant for patient´s safety in case cumulated. Please provide clarification on when this will occur, is it the number of changes, is it when the changes fit with a substantial modification listed in the table or something else? Proposed change: Please further specify or delete sentence.	Accepted. Line 702-703 ("The combination of different Art 81.9 changes can cumulate into a change that needs to be submitted as a substantial modification.") is deleted.
706-707	1.	Comment/Rationale: Please clarify that the text refers to quality amendments and not any amendment. Sections which are not relevant for the substantial modification may not be updated. "non-substantial changes" might be changed to "non-substantial modifications" Proposed change: At the time of an overall IMPD update or submission of a substantial quality modification the non-substantial quality ~~changes~~ modifications should be incorporated into the updated documentation, ~~which is required for the substantial modification~~."	Partly accepted The GL is on quality requirements and not any requirements. It is clarified in the GL that at the time of an IMPD update or a submission of a SM the NSM should be incorporated. Agreed: change modified to NS
708	1.	Comment/Rationale: "non-substantial changes" might be changed to "non-substantial modifications" Not clear how this should be done Proposed change:	Partly accepted. Changed to 'modifications'. Different formats are possible, depends on the extent of changes; can be a table.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		However, when submitting a modified IMPD, the sponsor should clearly identify which ~~changes~~ modifications are … Provide clarification what format to be used, e.g., table in the introduction	
712	1.	Comment/Rationale: Add a wording to clarify that this notification is not related to the type of change (i.e., SM or NSM) Proposed change: Provide clarification	Not accepted. Depends on when the change will become effective.
712	1.	Comment/Rationale: It is mentioned that substantial changes need to be submitted for ongoing clinical trials only. It would be appreciated to clarify whether the start of CT is related to the approval of the CTA and of Ethics Committee. Proposed change: Add clarification from when on a study is considered 'ongoing': from the time CTA/EC approval has been received or, e.g., when treatment of subjects has been initiated.	Accepted. The clarifying text 'i.e. after time of approval' is added.
718	1.	Comment/Rationale: Please ensure that the art. 81.9 non-substantial modifications column is consistent with the analogous guideline for chemical and pharmaceutical products, where it makes sense. Proposed change: Align the two guidelines where adding consistency.	Accepted. The guidelines have been aligned as far as possible.
719	1.	Comment/Rationale: Please clarify whether this change category applies to INN and trade name only, or to any change in the S.1.1 Nomenclature section of the IMPD. (Typically, in section S.1.1 Nomenclature of the IMPD, other	Partly accepted. Issue is not subject of this quality guideline. The requirement to notify a change of name or code of the active substance or IMP via Art 81.9 NSM has been deleted from the final version.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		compound/drug substance information is provided, such as new nomenclatures obtained during the course of drug development, e.g., generic name, IUPAC name, CAS Index name, CAS Registry number) Categorising a change in name within study documentation from company code to INN etc. requiring a proactive update via the Art 81.9 criteria is burdensome; preference would be for this to be a NSM to be updated with the next SM. Please clarify what is meant by "exchange of label". Is this intended to refer to an actual new and / or physical change to the label on the product / package? Proposed change: Please reconsider categorisation. See also 2nd comment in the general comments section.	
719	3.	Comment: Clarification of the change Proposed change (if any): (~~exchange of~~ change to the label)	Accepted.
720	1.	Comment/Rationale under SM: 2nd bullet point: considered redundant as covered by the first bullet point. 3rd bullet point: could clarification be provided if this relates to a safety or GMP compliance issue; is there not another route to highlight the issue rather than being reported as a quality substantial amendment? In this instance classification is based on a safety or GMP concern, however in general the expectation is that deletion of a site is considered non-substantial. Proposed change under SM: 1st bullet point: Add manufacturer and remove the 2nd bullet point.	Partly accepted. Not changed to NSM but reworded as follows; "Deletion of manufacturing, or testing site (for reasons impacting quality/safety of the IMP, or GMP compliance)."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		3rd bullet point: provide clarification	
720	1.	Comment/Rationale: Align with line 1267 re the new proposed text under Art. 81.9 NSM in the draft quality guideline for chem.-pharm. products. Although it is acknowledged that some analytical procedures used for the control of biological products may need significant oversight when transferred to other sites (due to their higher complexity or variability), addition or replacement of testing site for compendial methods or standard physico-chemical methods could be considered as non-substantial under Art.81.9 (see for example draft IMPD quality guideline on chemicals or variation guideline for marketed products). Addition or replacement of a testing site may be classified as NSM provided the same analytical methods are used at the new testing site and validation results have confirmed suitability of use of the methods at the new testing site. This ensures no impact on quality of the product. Consistent with line 723. Proposed addition under Art. 81.9 NSM or NSM: Addition or replacement of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated with comparable validation results according to the stage of development (including addition or replacement of a testing site for compendial tests)	Not accepted. Info on testing sites are not in the CTIS database, and current up to date information on the sites is required, therefore SM are required to keep the IMPD up to date.
720	3.	Comment: The revised general guideline permits the introduction of a drug substance testing sites where no changes are introduced to the specification or analytical methods as an Art 81.9 non-substantial amendment. It is not clear how the same change for biological	Not accepted. Info on testing sites are not in the CTIS database, and current up to date information on the sites is required, therefore SM are required to keep the IMPD up to date.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		products introduces greater risk to patients per the considerations outlined in lines 688 – 693. Proposed change (if any): Add "Replacement or addition of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated" as Art.81.9 non-substantial amendment.	
720 (+728)	1.	Comment/Rationale: Consider using of consistent wording: "testing site" vs "QC testing site" (see line 728) Proposed change: No change in line 720 but in line 728 (see there)	Accepted. QC testing site is the preferred term.
721	1.	Comment/Rationale: It is recommended that the list of SM changes be aligned as the counterparts to the relevant NSMs (and vice versa) to avoid ambiguity. For example, the NSM of "minor changes in the manufacturing process which do not require a comparability exercise" does not align with the SM of "changes to the cell culture conditions". In this case, a minor change to the cell culture conditions would still have to be notified as a SM even though it is considered minor. Alternatively, consider aligning the level of detail with the DP manufacturing process changes, which solely lists "significant changes to the manufacturing process" as an SM, and perhaps give examples of significant changes in each case (DS/DP)	Partly accepted. The final table has been updated.
720	2.	Comment: The splitting out of change in manufacturer between different companies compared to within the company is confusing, and use of different terminology for the same change (addition or replacement, vs change of manufacturer) is confusing. Suggest	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		combine into single bullet with harmonised wording as the change is the same, irrelevant of who owns the site. Proposed change: Addition or replacement of manufacturing site or testing site (including sites at a different location/address within a company) ~~Change of manufacturer or change of manufacturing site (within the same company)~~	
720	4.	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"*	Partly accepted. The guidelines have been aligned as far as possible.
721	1.	Comment/Rationale on SMs: The current proposals for substantial changes, when compared to the small molecule API guidance, maintains certain old distinctions between biologics and small, synthetic molecules. We would encourage much greater alignment between the biologics and API guidelines for post-approval changes to the quality section of the IMPD. Certain conditions or criteria described in the API guidance could equally apply to biologics to lower the regulatory reporting of appropriate, low risk changes. This is especially relevant when the data indicates no practically meaningful change to product quality, safety or efficacy. Proposed Changes:	Not accepted. Differences between small molecules and biologicals are reflected in the relevant guidelines.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Consider moving the following low risk changes that are supported by data to show no practically meaningful impact to product quality, safety or efficacy, from 'substantial change' to 'non-substantial change' in alignment with equivalent small molecule changes: Drug Substance Changes in cell culture conditions Removal of a redundant purification step Reprocessing	
721	3.	Comment: The opportunity to classify minor changes that do not require a comparability exercise as non-substantial amendments is welcome. However the list of substantial amendment should be clarified accordingly. Changes to the cell culture conditions that do not require a comparability exercise should be listed as non-substantial amendments. Other changes that are considered substantial would be inferred to need a comparability analysis. Proposed change (if any): changes to the cell culture conditions where no comparability exercise is required (e.g. change in feed schedule)	Not accepted. This is sufficiently covered by the general point; "minor changes in the manufacturing process which do not require a comparability exercise".
721	1.	Comment/Rationale under SM: 2nd bullet point: suggestion to be more precise. Also, the manufacture of a new working cell bank from the same MCB is considered a non-substantial change. We suggest categorizing the manufacture of a new Master Cell Bank as SM. 4th bullet point: Addition of a viral safety test corresponds to a tighter control on the product and should be considered as non-substantial. Suggestion to change wording.	Partly accepted. 2nd bullet, introduction of a new MCB and WCB is considered SM 4th bullet, viral safety: not agreed. 5th bullet, production scale: agreed. 6th bullet, cell culture conditions: partly agreed, wording revised. 7th bullet, not agreed.

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		5th bullet point: The bullet indicates that a change of production scale (upstream process) is to be regarded as substantial. Recommend adding clarification that this applies to the production bioreactor where the actual product is being made. A change in scale of the cell culture expansion stage might not be a substantial modification given the product is not produced during this stage of the process. It should be assessed on a case-by-case basis for potential impact of a scale change during the cell expansion phase. Also, the upstream manufacturing process of active substance involves many steps and the subject "change of production scale (upstream process)" is very broad as not all changes of production scale should be categorized as substantial modification. 6th bullet point: The bullet is too vague and should be clarified: only changes that are high risk and/or have potential to negatively impact product quality should be regarded as a substantial modification. Minor changes in cell culture conditions which don't impact CQAs could be categorized as non-substantial modification. This is in line with the non-substantial modification "minor changes in the manufacturing process which do not require a comparability exercise" 7th bullet point: Rephrasing to include changes that are not just addition/deletion and are not minor, i.e., the examples provided are not exhaustive. Minor changes would be captured as NSM's under the existing bullet "minor changes in the manufacturing process which do not require a comparability exercise" 8th bullet point: adding 'requiring' for clarification Proposed changes under SM: 2nd bullet point: new Master cell bank	8th bullet, agreed, wording revised; 'changes in the process conditions of any steps that have been identified as contributing to virus removal/inactivation, or that require new virus validation studies (viral clearance studies).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		4th bullet point: ~~Changes to~~ Deletion or replacement of the viral safety tests performed on cell banks or unprocessed bulk batches 5th bullet point: change ~~of production~~ in scale of the production bioreactor ~~(upstream process)~~ 6th bullet point: Major changes to the cell culture conditions impacting CQAs or having potential to negatively impact product quality or safety 7th bullet point: changes in the purification process (downstream)~~:~~ including (alternatively: e.g.,) the addition or removal of a purification step impacting CQAs or having potential to negatively impact product quality or safety 8th bullet point: changes in the process conditions of a step~~s~~ potentially effective on virus removal/inactivation, requiring new virus validation studies (viral clearance studies)	
721	2.	Comment: The wording around cell culture changes is very vague and could lead to unnecessary filings. Propose further clarity to specify changes that could be quality impacting. Proposed change: changes to the cell culture conditions that could impact critical product attributes.	Partly accepted. Wording updated; 'changes to the cell culture conditions potentially impacting on quality attributes'
721	1.	Comment/Rationale under NSM: Suggestion to add the introduction of a new WCB if prepared from an approved MCB. The approved WCB qualification protocol (including cell bank preparation method) will ensure that product quality is maintained when changing WCB.	Not accepted. Introduction of a WCB is considered a SM. Any reprocessing not described in the initial IMPD is considered a SM.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest adding examples of changes to equipment size and/or equipment type as a Non-substantial Modification (NSM) if supported by extensive comparability assessment. 3rd bullet point: If reprocessing is described and accepted in the initial submission, there is no need to report it as NSM. 5th bullet point: Changes to non-critical raw materials are listed as NSM, however changes to critical raw materials are not listed as SM – unless raw materials of biological origin are the only raw materials considered critical. Note: a definition of a critical raw material is not defined in the main body of the guideline (section S.2.3, lines 165-201), and this should be assessed in a phase-appropriate manner as part of the overall control strategy. It is therefore recommended that the agency clarifies what is considered to be a critical raw material, at what phase such criticality should be declared, and the list of NSM/SM be updated and aligned accordingly. Proposed change/addition under NSM: Addition: Introduction of a new WCB prepared from an approved MCB 3rd bullet point: ~~reprocessing if adequately described and accepted in the initial submission~~	
721	2.	Comment: The wording on viral clearance is a bit vague and should be related to steps that are known to clear/inactivate viruses, rather than steps for which the company makes no viral clearance claims but that could theoretically clear viruses (as this does not change the viral risk/safety assessment). Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		changes in the process conditions of any steps that have been identified as contributing to ~~potentially effective on~~ virus removal/inactivation, or that require new virus validation studies (viral clearance studies)	
721	3.	Comment: Clarification of the requirements around changes for steps impacting viral clearance. Proposed change (if any): changes in the process ~~conditions of steps~~ controls for a step with potential for effects ~~potentially effective~~ on virus removal/inactivation, requiring new virus validation (clearance) studies ~~(viral clearance studies)~~	Partly accepted. Wording updated as per above.
721	2.	Comment: A new Working Cell Bank derived from a clonal Master cell bank using established procedure should not be considered as a substantial modification Proposed change: New Master Cell Bank or a Working Cell Bank derived from a non-clonal MCB	Not accepted. Introduction of a new WCB is considered a SM.
721	3.	Comment: The reference to reprocessing is unclear. If reprocessing is not described in the IMPD, it is not clear if the change is to introduce the option to perform it, or to report that it has been performed, but if reprocessing is not described, and it has been performed, then a submission would be required before the reprocessed material could be used in the trial. Proposed change (if any):	Not Accepted. Regulators need to have the information before the batch is used. Either way a submission as SM is required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Introduction of the option to perform reprocessing at any step ~~not described in the IMPD~~	
721		In the manufacturing process of the active substance, 'changes such as New Cell Bank' (NCB) among others, are considered a Substantial Modification (SM) Comment: Regeneron agrees that when manufacturing the active substance, certain changes in the process should be considered as a substantial modification (SM) and concurs with the vast majority of those examples listed. One exception to this list is changes in a NCB, which should not automatically qualify as a SM. If a protocol with defined criteria for a new working cell bank (WCB) is included in the IMPD and approved by the Health Authorities, then implementing a new WCB that meets the required criteria should not constitute a SM, but could be considered a non-substantial change. This is a normal approach for commercial molecules. The WCB protocol ensures the new WCB is appropriately evaluated to ensure consistent product quality between cell banks, and therefore, there should be no impact to safety and efficacy. Regeneron would like to propose the Agency includes an exception from the SM list, and instead consider implementation of a new WCB as a non-substantial modification (NSM) if a protocol for qualifying a new WCB is already included in the IMPD and previously approved by the Health Authority. Proposed change (if any): N/A	Partly accepted. The text on cell banks is expanded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
722	1.	Comment/Rationale under SM: 1st bullet point: Consider moving reference to test methods to line 723 for test methods 1st bullet point: harmonise terms used: "test method" instead of "test procedure" 1st bullet point: amend wording to be consistent with 1st bullet point under NSM of line 723 2nd bullet point: Relocate under line 723 for test methods unless specification "parameter" is meant (proposal to differentiate between "test" (= test method) and "parameter"). Additionally, the difference between the two SM bullets is not clear as both changes will be based on supportive data. Consider to delete the second bullet. Align with guidance for chem-pharm products Proposed change/addition under SM: 1st bullet point: change in the specification, if acceptance criteria are widened ~~or test procedures are deleted or replaced~~ 1st bullet point: change in the specification, if acceptance criteria are widened or test ~~procedures~~ methods are deleted or replaced (unless the test method is replaced by an improved method which is suitable for use or validated according to the stage of development, and lead to comparable or better validation results) 2nd bullet point: ~~Replacement or deletion of a specification test based on supportive date~~ unless test is considered "parameter" Addition: Addition of specification or acceptance criteria ~~test(s~~) for safety/quality reasons	Partly accepted. The text has been revised and aligned with the chemical IMP guideline.
722	1.	Comment/Rationale under NSM:	Partly accepted. The revised text regarding test methods has been moved to section analytical

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Adding an acceptance criterion within the same test – if not safety driven – supports development of a consistent process that should be informed to CA without needing approval. Add "Deletion or replacement of test(s) due to compendial change" for consistency with chemical guideline (would apply mostly for general chapters) Add "Addition of test(s) with no safety reason" for consistency with chemical guideline Proposed change/addition under NSM: Tightening acceptance criteria or adding acceptance criteria to existing test specification (no safety reason) Addition: Deletion or replacement of test(s) due to compendial change Addition: Addition of test(s) with no safety reason	methods for control of the active substance (line 723).
722	3.	Comment: Second bullet is redundant, since the first bullet requires that changes to the specification, including deletion or replacement, be filed as a substantial amendment. The fact that supportive data are available does not change the classification of the change. Proposed change (if any): ~~Replacement or deletion of a specification test based on supportive data~~	Accepted. The revised text regarding test methods has been moved to section analytical methods for control of the active substance (line 723).
722	3.	Comment: Orthogonal tests could be added to the specification as non-substantial changes Proposed change (if any): Add "Addition of orthogonal assay (no safety reason)"	Accepted. The text has been amended and moved to section related to analytical methods for control of the active substance (line 723).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
723	1.	Comment/Rationale under SM: Reword first bullet point to add "replacement" Recommend remove 'new test conditions' because changed or new test conditions are covered by the changes under NSM It is not clear why this is considered a substantial modification as the intent for such a change would generally be to enhance quality testing of product Proposed change under SM: "~~New~~ Replacement of test method or new test conditions" ~~and new test conditions~~ Suggested to move to NSM	Partly accepted. The text for SM has been revised and aligned with the chemical IMP guideline.
723, 731	3.	Comment: Reference to new test conditions, without additional qualifiers, is contradicted by the list of changes that can be submitted as non-substantial amendments. Proposed change (if any): Introduction of new test methods ~~and new test conditions~~ Change to a test method that has the potential to affect the reported data (e.g. change in capture antibody in an ELISA)	Partly accepted. The text for SM has been revised, but example not included.
723	1.	Comment/Rationale under Art. 81.9 NSM: Relocation from SM in line 722 (see above) to Art. 81.9 NSM in line 723. The change would be informed to CA as art. 81.9 NSM together with supportive data, thus ensuring CA is informed by art. 81.9 NSM but no formal approval deemed necessary. Proposed addition under Art. 81.9 NSM: Replacement or deletion of a specification test based on supportive data	Not accepted. In principle, such changes should be approved following the assessment of the actual supportive data as they these changes may have potential effect on quality and safety therefore the submission of a SM is requested.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
723	1.	Comment/Rationale under NSM: The second bullet point under NSM is already covered by the first one. The fact that the updated analytical procedure is appropriately validated, with comparable or better validation results is sufficient to ensure the absence of substantial impact on product quality Addition of "update of the test procedure to comply with revised pharmacopoeia PhEur, USP or JP monograph" to align with draft quality guideline for chem-pharm products Consider whether it could be appropriate to include "addition of test(s) with no safety reason" as an example for NSM, as per lines 1269 (active substance) & 1279 (drug product) of the draft EMA/CHMP/QWP/318864/2021 Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning IMPs in Clinical Trials. Proposed change/addition under NSM: 2nd bullet point: ~~Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results~~ Addition: Update of the test procedure to comply with revised pharmacopeia PhEur, USP, or JP monograph	Partly accepted. The text for NSM has been revised and aligned with the chemical IMP guideline.
724	1.	Comment/Rationale: Where additional batches of drug substance/drug product are manufactured and the results are consistent with those already produced and meet the specification, then there should be no requirement to report this information. The batches that meet the specification is sufficient to assure patient safety in a clinical environment. Additionally, the section S.4.4 of IMPD clearly states that additional batches not yet manufactured at time of initial IMPD	Not accepted. This information is considered relevant.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		might be used, therefore section S.4.4 would not be required to be updated to include additional batches with same manufacturing process at the next substantial amendment. Suggest deletion. IMPD should only be updated with new batch data when a new clinical trial application is submitted Proposed change: ~~Additional batch data manufactured using the same process described in the IMPD unless it is requested otherwise~~	
725	1.	Comment/Rationale: The interpretation of "equivalence" is not clear: If the RS was manufactured with a different manufacturing process version, but comparability could be shown with a comparability exercise, would "equivalence" apply? In addition, that amended wording implies a new RS manufactured with a different process version requiring a comparability exercise, is considered as substantial amendment, and should be listed in the respective column. Proposed change under NSM: Introduction of new RS provided ~~equivalence~~ it was manufactured according to the same manufacturing process as the current RS, and comparability to the current RS has been established by following the same RS qualification protocol. Proposed change under SM: Introduction of new RS that requires a comparability exercise.	Partly accepted. Wording has been updated.
After line 725	1.	Comment/Rationale: Proposal to either add a category under "Changes to IMPD": "Container closure system of the active substance" or to add under line 726.	Partly accepted, the additional category for changes in "Container closure system of the active substance" was formed. Typical SM and NSM were introduced.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change/addition under NSM of the new category: Addition: Change to the container closure system without impact on stability conditions (e.g., same contact material, same surface/volume ratio, same filling ratio, etc.)"	
After line 725	2.	can a new line be added with Changes to IMPD: Container closure system of the active substance Comment: Propose addition of DS container closure changes to provide clarity on what is considered substantial vs non-substantial. Propose similar wording to DP (see line 733), plus addition of "product-contacting" as changes to non-product contacting components such as outer layer plastic films in bags should not be quality impacting even if there are minor changes in specification. Proposed change: Add to Non-Substantial Modification column (last column): Change of supplier (deletion, replacement or addition) of packaging components if the product-contacting material is identical and specifications are at least equivalent.	Partially accepted. Text modified.
726	1.	Comment/Rationale: Suggest adding examples for changes to active substance container closure. Suggest adding changes like "termination of stability study" due to end of study, "deletion or replacement of a test from stability protocol", "acceptance criteria of a stability protocol". Suggest adding the change of extension of protocol duration as NSM, since the conditions (tests and acceptance criteria) for retest period / shelf-life extension do not change; the appropriate stability of the	Partly accepted. Examples for changes to active substance container closure were introduced in a new section "Container closure system of the active substance". Wording of shelf-life extension based on the agreed protocol is updated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		material will still be demonstrated over the extended protocol duration, and any significant trends which may lead to an OOS result during the approved shelf life will be appropriately investigated. Other examples are reworded for clarity. Proposed change/addition under SM: 2nd bullet point: any extension of the shelf-life outside the agreed stability ~~protocol~~ criteria (storage conditions, tests and acceptance criteria) or without prior commitment Addition: Change to the type or material construction of the immediate packaging (comment: if a new category for ccs will be added this addition is recommended to be placed there) Addition: deletion or replacement of a test from the stability protocol Addition: change in the acceptance criteria of a stability protocol Proposed change/addition under NSM: Addition: Change to the size (but not construction) of the immediate packaging Addition: Termination of a stability study/protocol due to the completion or termination of the relevant clinical study(ies) Addition: Extension of protocol duration through additional timepoints to extend retest period without change of stability criteria (storage conditions, tests and acceptance criteria) After 2nd bullet point: 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	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		stability ~~protocol~~ criteria (storage conditions, tests and acceptance criteria Addition: A change in the stability test protocol to include more stringent parameters (e.g., additional assays or tightened specifications) Addition: Restriction of the storage conditions if not due to safety or stability concern	
726	1.	Comment/Rationale: It is noted that the requirement for a commitment to inform Competent Authorities of OOS results at the long-term storage condition has been removed. It is recommended to reinstall the following text from the previous version of the guideline: *"The applicant commits to inform Competent Authorities of unexpected stability issues in the ongoing study (including trends and OoS) and to propose corrective action as appropriate."*	Not accepted. This is already in the core guideline text.
727	1.	Comment/Rationale: Revised wording so clearer and consistent with draft quality guideline on chem-pharm medicinal products Should the 1st bullet point be expanded to state 'including changes in the active substance concentration and excipient composition' to reflect what had previously been included in the guideline (now deleted lines 666-667)? Or is the 1st bullet point now intended to refer to changes in excipient concentration? It is somewhat unclear how this first bullet point differs from the 2nd bullet point: is e.g., a different pharmaceutical form intended here in the 2nd bullet point (suspension vs solution for injection)? Please expand/ clarify or see next comment here below:	Accepted. Text modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest deleting 2nd bullet point under SM as considered covered by 1st bullet point Proposed change under SM: 1st bullet point: change to the qualitative or quantitative formulation including changes in the active substance concentration and excipient composition 2nd bullet point: ~~change of composition~~	
727	4.	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"*	Accepted. The guidelines have been aligned as far as possible.
728	1.	Comment/Rationale under SM: 1st bullet point: Please compare with line 720 for alignment of wording. 1st bullet point: Although it is acknowledged that some analytical procedures used for the control of biological products may need significant oversight when transferred to other sites (due to their higher complexity or variability), addition or replacement of testing site for compendial methods or standard physico-chemical methods could be considered as non-substantial under Art.81.9 (see for example draft IMPD quality guideline on chemicals or variation guideline for marketed products). 1st bullet point: Addition or replacement of a testing site may be classified as NSM provided the same analytical methods are used at the new testing site and validation results have confirmed suitability	Partly accepted. Most of these changes require confirmation/verification of GMP status, so should be retained as SM; i.e. Art 81.9 NSM is not appropriate. It is clarified that addition or replacement of an importation site that is not a QP certification site is NSM.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of use of the methods at the new testing site. This ensures no impact on quality of the product. Consistent with line 723. 2nd bullet point: is there not another route to highlight the issue rather than being reported as a quality substantial amendment? In this instance classification is based on a safety or GMP concern, however in general the expectation is that deletion of a site is considered non-substantial. 3rd bullet point: The current proposals for substantial changes, when compared to the small molecule API guidance, maintain certain old distinctions between biologics and small, synthetic molecules. We would encourage much greater alignment between the biologics and API guidelines for post-approval changes to the quality section of the IMPD. Certain conditions or criteria described in the API guidance could equally apply to biologics to lower the regulatory reporting of appropriate, low risk changes. This is especially relevant when the data indicate no practically meaningful change to product quality, safety or efficacy. Consider therefore moving the low-risk change of the 3rd bullet point when supported by data to show no practically meaningful impact to product quality, safety or efficacy, from SM to NSM in alignment with equivalent small molecule changes. Additionally, no significant impact on product quality or safety would be expected, given the low complexity of the manufacturing operations involved (see as comparison IA/IAIN category in the variation guideline for marketed products). 4th bullet point: The importation site should be considered independent of the QP release site as they may be different sites. As QPs are certified, the change of a QP release site should be informed to CA but not need approval as SM.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The change of an importing site that does not perform QP release should be reported as NSM or completely eliminated as not covered in the IMPD (section P.3.1 lines 457-460), and as not aligned with the MAA for CP ((https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf), in point 7.2.14. 4th bullet point: The QC testing sites are already captured in the 1st bullet point as testing site 'Addition or replacement of manufacturing site (including primary packaging) or testing site'. Alignment with quality guideline on chem-pharm medicinal products The addition of a secondary packaging/labelling site for authorised IMPs is proposed as NSM Proposed change under SM: 3rd bullet point: Move 'Adding or replacing a secondary packaging or labelling site to a site with a valid GMP' to NSM or Art. 81.9 NSM 4th bullet point: Move 'Addition or replacement of batch release certification site (QP certification)' to Art. 81.9 NSM. Delete "or QC testing sites" in 4th bullet point, and harmonise the terms (proposed: 'testing site' instead of 'QC testing site') Proposed change/addition under article 81.9 NSM: Addition: Addition or replacement of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated with comparable validation results according to the stage of development (including addition or replacement of a testing site for compendial tests) Addition: Addition or replacement of batch release certification site (QP certification). Proposed change/addition under NSM:	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Addition: Addition or replacement of importation site, if different from QP certification site. Addition: Addition or replacement of secondary packaging or labelling site with valid GMP status for authorised, non-modified test/comparator product. *(to be considered even more generally for all manufacturing steps -> see Annex IV of he CTR Q&A version 4 on change of source country which inherits a change of the manufacturer)*	
728	2.	Comment: Propose same addition as for active substance manufacturers regarding change in manufacturer between different companies compared to within the company (see line 720). Proposed change: Addition or replacement of manufacturing site (including primary packaging) or testing site (including sites at a different location/address within a company)	Not accepted. Covered by the existing wording.
728	2.	Comment: Physical importation is not identified as a manufacturing step within the guidance (P.3.1, line 457) and as such should be removed from the example to avoid confusion. Proposed Change: Addition or replacement of ~~importation~~, QP release or QC testing sites	Partly accepted. It is clarified that addition or replacement of an importation site that is not a QP certification site is NSM.
728	3.	Comment: The addition of a secondary packaging or labeling site for a biologic IMP introduces no or minimal risk to patients. This change should be treated as an Art.81.9 change. Proposed change (if any):	Not accepted. Changes requires confirmation/verification of GMP status so should be retained as SM; i.e. Art 81.9 NSM is not appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Move Addition or replacement of secondary packaging or labeling site with valid GMP status to Art. 81.9 Non-substantial Modification (NSM) column.	
728	4.	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.	Not accepted. Out of scope of this revision.
728	4.	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"*	Accepted. The guidelines have been aligned as far as possible.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
729	1.	Comment/Rationale under SM: What is considered a significant change? Some examples would be helpful. Lyophilisation or mixing would be a more complex change. In the guidance for chem-pharm products there is under SM (line 1276): "Scale-up for non-standard processes (e.g., lyophilization) or for large scale-ups". Scale-up of non-standard processes is proposed to be added under SM. Proposed addition (under SM): Addition: Scale-up for non-standard processes (e.g., lyophilization) Comment/Rationale under NSM: 1st bullet point: Proposal to revise wording as there is not always a need to demonstrate no effect, like for example a minor change in process parameter. For non-substantial modifications, it is unclear how the demonstration of no effect on product quality may have to be shown. Thus, proposal is to add wording for non-substantial modification like with DS (line 721). 2nd bullet point NSM: Regarding filling line scale ups as a NSM: does the 10 x multiplication factor limit apply also in this context? (Ref line 1276 of the draft EMA/CHMP/QWP/318864/2021 Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning IMPs in Clinical Trials Proposed change/addition (under NSM): 1st bullet point: Modifications of process parameters (same process process) where no effect on product quality is ~~demonstrated~~ expected Addition (following line 721): Minor changes in the manufacturing process which do not require a comparability exercise.	Not accepted. The guideline wording is considered sufficient in both instances.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
729	2.	Comment: Propose addition of some bullets to Non-substantial Modification column (last column) to ensure alignment between drug substance (see line 721) and product reporting categories Proposed change: Addition or tightening of IPC if not due to safety reasons Reprocessing if adequately described and accepted in the initial submission	Not accepted. The guideline wording is sufficient. The addition or tightening of IPC does not always need to be reported so long as it is sufficiently managed in the PQS.
729	2.	Comment: Propose to provide examples for the substantial modification category to align better with the bulleted examples provided in line 721 for drug substance Proposed change: Significant changes to the manufacturing process Changes leading to the occurrence of new impurities Any reprocessing not described in the IMPD	Not accepted. Current guideline wording is considered sufficient, these specific examples are not required.
730	1.	Comment/Rationale under SM: 1st bullet point: Further clarification about the deletion of tests would be needed. It is stated that the deletion of a test based on supportive data is considered as SM. However, how should the replacement of a specification test (parameter) be assessed that has been demonstrated to be not critical and/or stability indicating? Could it be considered as an Art. 81.9 NSM? It is suggested to widen the scope to cover this case. 1st bullet point: consider reference to test methods to be captured in line 731. Additionally, it is not clear what the difference between changes in specifications ("test procedures are deleted") and	Partly accepted. The text has been revised and aligned with the chemical IMP guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"replacement or deletion of specification test based on supportive data" is. 1st bullet point: Same comment as in line 722: Consistent wording to describe analytical procedures as part of a specification parameter is desirable: replace "procedure" with "method" 1st bullet point: proposed changed wording for alignment with line 723 Proposal to add wording of draft guidance for chem-pharm products Proposed change/addition under SM: 1st bullet point: Change in the specification, if acceptance criteria are widened or ~~test procedures are~~ deleted ~~or replaced~~ 1st bullet point: change in the specification, if acceptance criteria are widened or test ~~procedures~~ methods are deleted or replaced (unless the test method is replaced by an improved method which is suitable for use or validated according to the stage of development, and lead to comparable or better validation results); alternatively: remove the word "replaced" 2nd bullet point: ~~• Replacement or deletion of specification test based on supportive data~~ Addition: Addition of specification or acceptance criteria for safety/quality reasons Comment/Rationale under Art. 81.9 NSM: Consistency with chemical guideline (same proposal for line 722). Proposed change/addition under Art. 81.9 NSM: Addition: Deletion or replacement of test(s) due to compendial change	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment/Rationale under NSM: Addition of acceptance criteria within the same test – if not safety driven – supports development of a consistent process that should be informed to CA without needing approval Please consider including "addition of test(s) with no safety reason" as an example for NSM, as per lines 1269 (active substance) & 1279 (drug product) of the draft EMA/CHMP/QWP/318864/2021 Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning IMPs in Clinical Trials. (see also 722) Proposal to add wording for alignment with line 723 Proposed change/addition under NSM: Tightening acceptance criteria or additional acceptance criteria to existing test specification (no safety reason) Addition: Addition of test(s) with no safety reason (alignment with line 722) Addition: Test procedures are replaced by an improved method which is suitable for use or validated according to the stage of development, and lead to comparable or better validation results (alignment with line 723)	
731	1.	Comment/Rationale: The change "Replacement or deletion of a specification test …) in line 730 should be moved to line 731, with considering that the replacement of a test of a parameter that has been demonstrated to be not critical and/or stability indicating (i.e., 'based on supportive data' should be NSM or art. 81.9 NSM. SM: It is unclear what "new test conditions" means when comparing with the NSM changes to analytical methods. Rewording proposed to	Partly accepted. The text has been revised and aligned with the active substance part and with the chemical IMP guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Replacement of test method or new test conditions" (see also proposal for line 723) Recommend to remove 'new test conditions' from the SM bullet, because test conditions are basically covered under NSM (same comment provided for line 723) Proposed change/addition under SM: ~~New~~ Replacement of test method~~s~~ ~~and~~ or new test conditions" ~~and new test conditions~~ Comment/Rationale under NSM: Align with quality guideline for chem-pharm products Wondering if the 2nd bullet point under NSM ("variation of the method …) is redundant as considered covered by the 1st bullet point. The fact that the updated analytical procedure is appropriately validated, with comparable or better validation results is sufficient to ensure the absence of substantial impact on product quality. (see also comment provided for line 723) Proposed change/addition under NSM: Addition: Replacement or deletion of a specification test based on supportive data Addition: Update of the test procedure to comply with revised pharmacopeia PhEur, USP, or JP monograph Consider deleting the 2nd bullet point: ~~Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results~~	
732	1.	Comment/Rationale: Where additional batches of drug substance/drug product are manufactured and the results are consistent with those already	Not accepted. Particularly in early development, where batches are few, information on additional batches provides assurance of manufacturing

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		produced and meet the specification, then there should be no requirement to report this information. The batches that meet the specification is sufficient to assure patient safety in a clinical environment. IMPD should only be updated with new batch data when a new clinical trial application is submitted Section P.5.4 of IMPD clearly states that additional batches not yet manufactured at time of initial IMPD might be used. Proposed change under NSM: Deletion suggested	consistency and should be available for assessment. Knowledge on batches manufactured is also essential for pharmacovigilance.
733	1.	Comment/Rationale: Align terminology regarding "primary" and "immediate" packaging with main document text. "Immediate packaging" is correct the term as defined in Article 2.1. of CTR536/2014. SM: Proposal to add components in contact with product The 1st bullet point under NSM is proposed to be deleted as secondary packaging is not required to be detailed in the IMPD (section P.7, lines 573-585) The 2nd bullet point under NSM is proposed to be deleted or revised as proposed below as the IMPD does not reflect this degree of detail. Suppliers are not required to be detailed in the IMPD (section P.7, lines 573-585) Proposed change: SM: Changes to immediate packaging and product contact components of the immediate container closure system NSM: Change ~~of supplier~~ (deletion, replacement or addition) of immediate packaging or immediate packaging component(s) if the material is identical and specifications are at least equivalent.	Not accepted. Guideline wording is sufficient. NSM point refers to supplier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
733	2.	Comment: Propose addition of "product-contacting" as changes to non-product contacting components such as aluminium flip-caps should not be quality impacting even if there are minor changes in specification. Proposed change: Change of supplier (deletion, replacement or addition) of packaging components if the product-contacting material is identical and specifications are at least equivalent.	Not accepted. The terms 'primary' and 'secondary' packaging are used.
733	3.	Comment: Current wording is imprecise. Proposed change (if any): changes to ~~immediate~~ primary packaging	Accepted. The terms 'primary' and 'secondary' packaging are used.
734	1.	Comment/Rationale: Clarification is needed how to present the changes with respect to the device constituents part of the drug device combination products. 1st bullet point SM: Please clarify if this is related to the device constituent part of the integral drug-device-combination product (e.g., different finger plate or plunger rod), or related to listed administration devices (e.g., syringes, in-line filters etc.) 2nd bullet point SM and under NSM: in alignment with EMA Q&A Answer 2.6. of the June EMA Q&A document for devices & medicinal products, please add "intended purpose". Suggest adding "Medical device or device part" - to make it more clear and to harmonise wording with new EMA guideline on "Quality documentation for medicinal products when used with a medical device".	Partly accepted. The table entry for changes to medical devices has been simplified and the text relating to medical devices (chapter 2, section P.7) has been updated with reference to the Medical Device Regulation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please provide some examples of changes impacting on the quality, safety and/or efficacy for medical devices, to help the evaluation Proposed change under SM: 1st bullet point: Suggest adding examples in the substantial and non-substantial categories (e.g., syringes, in-line filters, different finger plate or plunger rod etc.) 2nd bullet point: Changes to a medical device (design or intended purpose) registered in the IMPD …. Proposed change under NSM: changes to a medical device (design or intended purpose) registered in the IMPD which is not considered to impact ….	
735	1.	Comment/Rationale: Proposal to align with the requirements for drug substance It is noted that the requirement for a commitment to inform Competent Authorities of OOS results at the long-term storage condition has been removed. It is recommended to reinstall the following text from the previous version of the guideline: *"The applicant commits to inform Competent Authorities of unexpected stability issues in the ongoing study (including trends and OoS) and to propose corrective action as appropriate." (see also similar comment in line 726)* Proposed addition (under SM): changes in the approved storage conditions	Partly accepted. Section is aligned with active substance section.
735	4.	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.	Not accepted. Proposal is not clear. Extension of shelf life is already addressed in the guideline text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	