EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/CHMP/QWP/693578/2021
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials' (EMA/CHMP/QWP/545525/2017 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	ACRO (Association of Clinical Research Organizations)
2	Bluepharma – Industria Pharmaceuitica, S. A.
3	EFPIA
4	Gossamer BioService Ltd.
5	Takeda

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
`1	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 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	

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2	It would be very helpful to add a section dedicated to the medicinal products when used with a medical device.	We agree that addition of a section dedicated to medicinal products used with medical devices would be helpful however, this revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
3	A comparison of the Chemical and Biological Quality Guidelines shows apparent inconsistencies regarding changes which are considered relevant to the supervision of a trial. An example of this is the case of reporting of analytical testing sites and container closure systems. In relation to the quality information submitted, it should be considered that the information falling under Art 81.9 would be limited to the Name/Code, pharmaceutical form, and strength. This would be consistent with the released CTIS (Clinical Trials Information System) structured data forms content requirements.	Our aim is to keep the inconsistencies between the biological and chemical quality guidelines minimal however, sometimes it is not possible to have a harmonized approach as the biological and chemical drug products are different types of products and the specifics of each category has to be taken into account.
3	***1.5 General considerations /2.1.S.2 Manufacture / 2.2.1.S.2.3 Control of materials*** Generally, the guidance covers the situation where the active substance is an existing compendial active substance where most of the information could be covered by referencing to the corresponding monograph or CEP. However, when the information of an active substance is supported by an ASMF issued by a third party, some of the information requested in the guidance related to the synthesis of the drug substance, including reagents, solvents, catalysts and processing aids belongs to the Restricted part of the ASMF. Actually, the ASMF holder usually only provides to the sponsor with a general flow chart of the active substance synthesis. Additionally, it would be appreciated to differentiate between existing and new active substances which are supported or are going to be supported by an ASMF issued by a third party. For existing active substances, it is likely that the corresponding ASMF has not been submitted yet at the clinical development stage, so, neither letter of Access nor	This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.

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	detailed restricted information will be available to be submitted by the time of IMP. Furthermore, for new active substances it is even more likely that the corresponding ASMF has not been compiled yet at the clinical development stage, so, the same as for the existing active substances explained above happens. We fully understand EMA position on following the ASMF procedure, but we would appreciate additional wording in the guidance on how to overcome the lack of confidential information which is part of the intellectual property of the supplier either when the ASMF has not been yet compiled or submitted. Additional clarification is also welcomed if the review of the ASMF in parallel to the IMPD will have any impact on the timelines of the CTA procedure.	
3	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 is 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 guiding principles would be helpful.	As the guideline Chapter 9 states, non-substantial changes relevant to the supervision of the trial (Art 81.9 change) aim to update certain, specified information in the CTIS without the need for a 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. Further examples of changes related to the quality are listed in the table.
3	The proposed revisions in section 9. are appreciated as giving more concrete guidance on classification of changes.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
264-269	3	Comment/Rationale: It is proposed to add relevant requirements for radiopharmaceuticals as the current content of the guideline does not provide enough clarity for the quality documentation required for chemical precursors and radionuclides used in the radiopharmaceuticals. The quality details expected for Chemical precursors are same as for an active substance and therefore ASMF and CoS EDQM should also be applicable for the chemical precursors. The level of quality details required for radionuclides used in the therapeutic radiopharmaceuticals are not clear enough. Clarity should be emphasized on the quality details required for radionuclides which are starting materials for the radioactive drug substance, and although they are in the precursors category, the level of details differs when compared with chemical precursors. Proposed addition (after line 269): The reference to an Active Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicines is also acceptable for chemical precursors (non-radioactive precursors) used in the radiopharmaceutical drug products. The radio-nuclides used in the therapeutic and diagnostic radiopharmaceuticals are not considered drug substances and therefore an Active Substance Master File or a Certificate of Suitability are not applicable. The radio-nuclides are to be considered starting materials for therapeutic and diagnostic radiopharmaceuticals and the details required should follow the requirements for starting materials.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
271-274	3	Comment/Rationale: • It is proposed to add relevant requirements for radiopharmaceuticals to avoid HA assessment duplication for same quality information already assessed and approved under an already granted marketing authorization.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: If the Active substance or Chemical Precursors (non-radioactive precursors of radiopharmaceuticals) used is already authorised in a drug product within the EU/EEA or in one of the ICH-regions, reference can be made to the valid marketing authorisation. If a radio-nuclide precursor is already authorized within the EU/EEA or in one of the ICH-regions as for the radiolabelling of carrier molecules specifically developed and authorised for radiolabelling with the specific radionuclide, reference can be made to the valid marketing authorisation. A statement from Marketing Authorisation Holder or drug substance or chemical precursor manufacturer should be provided that the active substance or chemical precursor has the same quality as in the approved product	
288	1	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.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
397-398	1	Comment: The "relevant guidelines" considered appropriate by the EMA should be referenced. Proposed change (if any): Include appropriate references.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
446	3	Comment/Rationale: Consideration should be given to where other updates in the document are required to support management of changes during clinical trials. For example, earlier in the guidance, the statement '*The manufacturing process used for each batch should be assigned as stated under 2.2.1.S.2.2.*' should be revised to also include reference to Section S.2.6 as follows: '*The manufacturing*	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.

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		process used for each batch should be assigned as stated under 2.2.1.S.2.2 and 2.2.1.S.2.6.' This is based on the rationale that the current manufacturing process for the batches of drug substance intended for clinical use is positioned in Section S.2.2 whereas the prior manufacturing process(es) for batches of drug substance used in non-clinical studies and/or previous clinical studies are positioned in Section S.2.6.	
465	3	Comment/Rationale: Predictive stability approaches to justify retest date or shelf life should be included. Proposed change: Add predictive stability approaches as example for setting the initial re-test period.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
523-524	3	Comment/Rationale: The site of QP release is a mandatory part of the EudraCT application form and as such it is recorded in that form for each CTA. The CMC portion of the IMPD (P.3.1) however is submitted for global studies, including countries where QP release sites may not be relevant. In order to harmonize CMC content globally, and avoid duplication and/or inconsistencies, it is proposed that the site for QP release remains only in the binding element of the EudraCT application form. Additionally, the request to provide details on the site(s) responsible for import in the EEA is neither aligned with the MAA for Centralised Procedure (see 7.2.14. of https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf), nor with the quality guideline for biological products. Proposed change: Delete the requirement that 'Site(s) responsible for import or/and QP release in the EEA should be also stated.'	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.

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523, 761, 975 and 1275	1	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 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.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
675	3	Comment/Rationale: Accelerated Stability Assessment Programs should be accepted for setting the initial shelf life. Proposed change: Add 'predictive stability approaches, i.e., Accelerated Stability Assessment Programs (ASAP)' as example for setting the initial shelf life	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
713 -720	3	Comment/Rationale: In some cases, the non-IMP used as a concomitant medication of the IMP for some clinical trials are commercialised in different countries with different MA-holders and MA-numbers. The investigator of each country enrolled in the CT could select the non-IMP commercially available in that country. The guidance state that "it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA". However, according to the situation explained above it is possible that this information will not be available by the time of IMPD submission.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.

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		Proposed change: Advice on how to manage this situation is desirable, e.g., by referencing to Annex I of the CTR536/2014 and/or Annex IV of the CTR Q&A.	
724	1	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.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
981-983	2	Comment: Section Batch Formula states that "Where relevant, an appropriate range of batch sizes may be given." Proposed change (if any): Text clarification is suggested to make sure when it is necessary to provide the range of batch size.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
1074	3	Comment/Rationale: The table of classification below line 1265 is obviously applicable to IMP, but not clearly indicative whether it is applicable to placebo. Proposed change: Add a statement to clarify at the beginning of the Placebo section if Placebo is subject to the requirements as detailed in the table starting on line 1266.	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
1186	3	Comment/Rationale: Please make sure that chapter 9 is in line with the corresponding guidelines on biologicals Proposed change: Align the two guidelines.	REJECTED Our aim is to keep the inconsistencies between the biological and chemical quality guidelines minimal however, sometimes it is not possible to have a harmonized approach as the biological and chemical drug products are different types of products and the

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			specifics of each category has to be taken into account. Please note that these guidelines are not intended to be fully identical, but rather that they are not contradictory.
1189-1191	3	Comment/Rationale: Auxiliary medicinal products usually are authorised Medicinal Products with a Marketing Authorisation. 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 in line 1190: "In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP/unauthorised auxiliary medicinal product at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions"	DISMISSED This revision is focused only on chapter 9 of the guideline to align the categories of changes made to the IMPD with the Regulation EU No 536/2014 due to limited time allocated to the revision.
1215	3	Comment/Rationale: Further clarifications on the difference between an 81.9 NSM and a NSM would be appreciated Proposed change: Please consider to provide more clarification.	REJECTED The differences between each category are described in chapter 9 and further examples of changes related to quality are listed in the table. Additional guidance will be provided in a separate Q&A document prepared by the Commission.
1229	3	Comment/Rationale: Further guidance could be given on the definition of 'substantial' with regards to impact on patient. Currently this is quite subjective and could be open to interpretation by sponsors and member states, and therefore impact whether changes are submitted under the correct assessment especially with the new Art 81.9 definition ….*substantial impact on the safety and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial*	REJECTED Examples of changes related to the quality are listed in the table and further guidance will be provided in a separate Q&A document prepared by the Commission. Additionally, the sponsor is recommended to consult the Reporting Member State in case of doubt.

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		Proposed change: Please consider providing more guidance on this matter.	
1236	1	Comment: Typographical error. Proposed change: "are concept" should read "are a concept".	ACCEPTED
1236	3	Comment/Rationale: Further clarification whether and if so, how a single change according to 81.9 should be submitted. Proposed change: Provide clarification	REJECTED A guidance how to submit an Art 81.9 change is not a quality related issue. Additional guidance will be provided in a separate Q&A document prepared by the Commission.
1236 - 1245	1	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	REJECTED This is not a quality issue but rather it is related to functioning of CTIS and is general in nature. Additional guidance will be provided in a separate Q&A document prepared by the Commission which refers to this guideline for quality related changes.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		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".	
1236-1245	3	Comment/Rationale: • Clarify the sentences/paragraph as difficult to read/comprehend in the current state. • As this is a quality guideline it is unclear how quality substantial or non-substantial changes can impact *the supervision of a trial* or *the patients' rights and/or data robustness.* • It is unclear how non-substantial quality changes should be documented. Proposed change/addition: • Changes relevant to the supervision of the trial (Art 81.9 change) are a concept introduced under the CTR. The aim of the addition of this concept/category is to update specific information in the Clinical Trial Information System (CTIS) without the need for a substantial modification application. The information being updated under this concept is necessary for oversight but does not have a substantial impact on patients' safety, rights, and/or data robustness. … • Please provide some clarification to the 2nd bullet point under Comment/Rationale. • Addition: A list of Quality/CMC changes categorised as Art 81.9 non substantial changes should be permanently updated in the EU database (CTIS), such changes would be considered as a notification and considered approved/ authorised at the time of provision/ upload in the CTIS.	• PARTIALLY ACCEPTED: The sentence has been revised in line with other comments: "Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are *a* concept introduced under the CTR, which aims to update information in the CTIS without the need for *a* 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." • REJECTED: Further examples of changes related to quality are listed in the table. The wording is a definition used by the Commission in the related Q&A document.

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			• REJECTED: This is not a quality issue but rather it is related to functioning of CTIS and is general in nature. Additional guidance will be provided in a separate Q&A document prepared by the Commission which refers to this guideline for quality related changes.
1236-1245	3	Comment/Rationale: Does GMP documentation (e.g., GMP certificate, Manufacturing and Import Authorization) fall under "specified information in CTIS"? Proposed change: 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.	REJECTED Additional guidance will be provided in a separate Q&A document prepared by the Commission which refers to this guideline for quality related changes. The sentence has been revised for more clarity and in line with other comments: "Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are *a* concept introduced under the CTR, which aims to update information in the CTIS without the need for *a* 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."
1236	5	Comment: Typographical correction Proposed change (if any): Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are a concept introduced under the CTR…	ACCEPTED
1238, 1243 and 1245	1	Comment: Typographical error.	ACCEPTED

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: "an" in each of these lines should read "a".	
1244-1245	3	Comment/Rationale: We suggest to provide clarification on when this will occur. We understand that the Art 81.9 changes have the aim to update certain specified information in the CTIS for the oversight and do not have a substantial impact on patient's safety and rights and/or data robustness. These changes are not seen to have an interaction between each other's which may justify a higher change category. 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: Either delete the sentence "The combination of different Art. 81.9 changes can cumulate into a change that needs to be submitted as an SM" or provide clarification how these changes might cumulate to qualify as SM.	ACCEPTED The last sentence has been deleted. Additional guidance to this issue will be provided in a separate Q&A document prepared by the Commission which refers to this guideline for quality related changes.
1244	5	Comment: Additional clarity on, or examples of the types or combinations of art. 81.9 changes that could cumulate into a change that needs to be submitted as a substantial amendment would be helpful. It appears that making multiple separate updates to the database would circumvent the requirement. Proposed change (if any): Examples added	NOT APPLICABLE The sentence has been deleted (see comment above)
1251 to 1252	3	Comment/Rationale: Clarification that the text refers to quality amendments and not any amendment Proposed change: At the time of an overall IMPD update or submission of a substantial quality modification the non-substantial quality changes should …	REJECTED The proposed wording could be misleading. It could be interpreted that non-substantial quality changes could be submitted only with quality substantial amendments, which is not the case.
1256	3	Comment/Rationale: Provide clarification	ACCEPTED The following wording will be used for more clarification:

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		<u>Proposed change:</u> Add a wording to clarify that this notification is not related to the type of change (i.e., SM or NSM)	"When *any quality modification* will become effective with the start of a new clinical trial…"
1258	3	<u>Comment/Rationale:</u> 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 RA and EC approval. <u>Proposed change:</u> 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 following wording will be used for more clarification: "*Submissions* of substantial modifications are only necessary for changes *to* ongoing clinical trials *(i.e., after time of approval)*."
1265	1	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."	ACCEPTED
Column headline above line 1266	3	<u>Comment/Rationale:</u> Please ensure that the headlines are harmonised between the two guidelines. <u>Proposed change:</u> Use the same terms as in the table headline of the guideline for biological IMPs	ACCEPTED
1266-1282	2	Comment: Changes in the impurities profile are not included in the table of Section 9. Proposed change (if any): Inclusion of "additional or new impurity" in the table of Section 9 as a substantial amendment.	REJECTED The table is not an exhaustive list of changes, in case of doubt the sponsor should consult the Reporting Member State. This particular example has to be assess on case by case

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			basis whether there is an impact on product quality/safety.
1266-1282	2	Comment: Changes in CoAs for new batches of the medicinal product are not included in table of Section 9. Proposed change (if any): Inclusion of CoAs of new batches manufactured with the approved process in the table of Section 9 as a non-substantial amendment.	REJECTED The table is not an exhaustive list of changes, in case of doubt the sponsor should consult the Reporting Member State
1266	3	Comment/Rationale: 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, and the timeframe for the updating to be done is not clear. In addition, 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 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. Preference would be a NSM to be updated with the next SM. Proposed change: Move "Change from company code to INN or trade name during ongoing clinical trial (exchange of the label)" from Art. 81.9 NSM to NSM	NOT APPLICABLE In line with BWP the whole row has been deleted as this type of change is not common
1267	1	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"	PARTIALLY ACCEPTED Our aim is to keep the inconsistencies between the biological and chemical quality guidelines minimal however, in this case it is not possible to have a harmonized approach as the biological and chemical drug products are different types of products and the specifics of each category has to be taken into account. Please note that these guidelines are not intended to be fully

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			identical, but rather that they are not contradictory. For similar examples the wording has been aligned.
1267	3	Comment/Rationale: • There is some room for clarification by small changes in the SM and the NSM column. For the categorisation of testing site changes (where method transfer has taken place) under Art. 81.9 it is implied that such changes are specifically relevant to the supervision of the study. In contrast, where a DS (drug substance) manufacturer changes within the same company a non-substantial change can be applied (as is the case under the current guidance). • 2nd bullet point under SM: It is not clear why "safety reason" is mentioned as reason. Shouldn't it be just "GMP non-compliance" that could lead to patient safety issues? Proposed change under SM: • 1st bullet point: Addition of or change to a new manufacturer (outside the company). • 2nd bullet point: Deletion of manufacturing or testing site (for ~~safety reason,~~ GMP non-compliance) Proposed change under Art. 81.9 NSM: Changes in testing sites, where method validation has been performed, should be classified as non-substantial changes. Proposed change under NSM: • name or address change of the drug substance manufacturer	Proposed changes under SM: • PARTIALLY ACCEPTED: the proposed wording has been revised: "Addition of or a change to a new manufacturer (outside the company *or within the company but in a different country*)" • REJECTED: GMP non-compliance does not cover all issues that could impact the quality or safety. Additionally, the wording has been aligned with BWP: "Deletion of manufacturing or testing site (for *quality*/safety, GMP-non-compliance) Proposed change under Art. 81.9 NSM: ACCEPTED Proposed change under NSM:

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			• PARTIALLY ACCEPTED: the proposed wording has been revised "name *or address* change of the drug substance manufacturer *provided that the manufacturing site and all manufacturing operations must remain the same*"
1268	3	<u>Comments/Rationales under SM:</u> • 2nd bullet point: Change the term "Extension" to "Widening" for consistency within and among other guidelines. • 3rd bullet point: Not all physiochemical changes in the DS have a quality impact on a solid oral dosage form; for example, if a spray dried dispersion is used in the drug product process the DS particle size or crystal form may not be an impactful change. <u>Proposed changes/additions under SM:</u> • Change: ~~Extension~~ Widening of the process parameters or in-process control acceptance criteria with impact on product quality and safety • Addition: Widening of method validation criteria <u>Comments/Rationales on NSM:</u> • Subjective criteria will cause uncertainty with Sponsors and should be removed or better defined with criteria. A 'slight modification' could expand a range which confuses with a substantial amendment. • A non-substantial change should include changes where validation data generated in support of the change meet the same or more restrictive criterion as previously approved in the IMPD. Only if the same validation criterion cannot be met or if a new impurity is detected should it be a substantial change. This is in alignment with Draft ICH Q14 concepts.	<u>Proposed changes under SM</u>: • ACCEPTED • NOT ACCEPTED: not related to the manufacturing process but rather test methods. Additionally, this is a very specific case and the table is not an exhaustive list <u>Proposed changes under NSM</u>:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• Reprocessing steps without any additional safety risk for the clinical trial should be allowed for under NSM. Proposed changes/additions under NSM: • Modification of the process parameters such that there is no impact to product quality (same process, similar solvents, …) or alternatively: "(same process and synthetic route, albeit with possible modifications in solvents, reagents, catalysts, temperature, pressure, reaction time, or stoichiometry that do not impact the physicochemical properties or the impurity profile of the active substance)" • Addition: Changes in the physiochemical properties without influence on the quality of the IMP (e.g., particle size distribution for highly soluble drug, particle size distribution and/or polymorphism for a drug product that contains a spray dried dispersion). • Addition: Minor changes to an analytical method included in the IMPD for which any validation data to support the change meets the same or more restrictive criterion as the pre-change method validation. No new impurities compared to non-clinical batches are detected. • Addition: Addition or tightening of IPC with no safety reason (rationale: alignment with quality guideline for biologicals) • Addition: Reprocessing e.g., repetition of a purification step not described in the IMPD	• PARTIALLY ACCEPTED: the proposed wording has been revised "Modifications of the process parameters *and widening of in-process acceptance criteria* such that there is no impact to product quality (same process and synthetic route, albeit with possible *slight* modifications in solvents, reagents, catalysts, temperature, pressure, reaction time or stoichiometry that do not impact the physicochemical properties or the impurity profile of the active substance)" • ACCEPTED • REJECTED: not related to the manufacturing process but rather test methods. Similar example has been included in the test method section in line with BWP guideline • ACCEPTED • PARTIALLY ACCEPTED: the proposed wording has been revised. "*Addition of a reprocessing not described in the IMPD (e.g., repetition of a purification step)*"
1269	3	Comment/Rationale: • General: shouldn't any change related to a **test** be better captured under line 1270 (test methods)? • 1st bullet point under SM: Change the term "Extension" to "Widening" for consistency within and among other guidelines.	• General comment – REJECTED: The current wording refers to whether tests are included in the specification, and their limits within the specification

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• SM: The addition or expansion of an acceptance criterion to the existing spec (i.e., instead of "conforms to standard" to "conforms to standard with a specified parameter range e.g., the chromatographic pattern conforms to the reference standard with a relative retention time range of the sample peak to ref. std peak of 0.9 to 1.1) should be a NSM if within the same test and no safety reason. • 3rd bullet point under SM: the example given is for safety reason, it is therefore proposed to remove "quality reason". • Art. 81.9 NSM: Specific additional oversight for the deletion of a test because of a compendial change does not relate to the trial subject risk. • NSM: Provide examples of tests that can be added as non-substantial changes Proposed change under SM: • 1st bullet point: ~~Extension~~ Widening of acceptance criteria • 3rd bullet point: Addition of test(s) for safety~~/quality~~ reasons, e.g., addition of mutagenic impurity control Proposed change under Art. 81.9 NSM: • Move "Deletion of test(s) due to compendial change" to NSM and add "or replacement" Proposed additions under NSM: • Addition: Addition or expansion of an acceptance criterion to the existing test specification within the same test with no safety reason • Addition: Deletion or replacement of a test due to compendial change	Proposed changes under SM: • ACCEPTED • REJECTED: addition of mutagenic impurity was given as an example only, and it is related not only to safety but also to quality. Proposed change under Art. 81.9 NSM: • ACCEPTED – the example has been moved to NSM but the wording has been revised in line with BWP guideline Proposed changes under NSM: • REJECTED: expansion of the acceptance criterion is the same as widening of acceptance criterion which is a SM

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			• PARTIALLY ACCEPTED: the wording has been revised in line with BWP guideline. "*Addition*, deletion or replacement of a *specification parameter* due to compendial change."
1270	3	<u>Comment/Rationale:</u> • The draft quality guideline on biologics (lines 723 & 731) provides for analytical method improvements or variations which require method validation (suitable to the stage of development), but which lead to improvements in the analytical method with established comparable or better validation results as **non-substantial modifications**. It is kindly requested to apply a similar approach to small molecules, rather than requiring a substantial amendment due to a need to perform additional validation following changes to an analytical method. • The text proposed regarding method validation is more restrictive than the current Guidance. Where a method change results in revalidation and improvement such that validation results are better or equivalent to the current state then this change should be considered as non-substantial as allowed under the current Guidance. • Provided the analytical principle remains the same, and the changes brought to the analytical procedure lead to comparable or improved performance as shown by appropriate validation, there is no significant impact on product quality and the changes should be reported as non-substantial. • Wording for both items is "New test method (e.g. NIR instead of HPLC)" but the 'instead' reads like a replacement of an existing test. With this rational, an actually "new" test would not be identified as a substantial change. Perhaps "Different test" might be clearer.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• For reference standards, include a common change as a NSM in-line with the newly added provision found within the companion, updated EMA IMPD guidance for biologics. • Advice is sought for the typification of changes related to obsolete test or test that do not longer provide relevant information of the DS. <u>Proposed changes/additions under SM:</u> • Addition: Change in analytical technique (e.g., NIR instead of HPLC). • Change: "…or method changes requiring new validation providing results that are not better or equivalent to the approved method, and/or impact the control strategy or specification." • Change: New or different test method (e.g., NIR instead of HPLC) or method changes requiring new validation <u>Proposed changes/additions under NSM:</u> • "Minor changes ... for which no additional validation is necessary. Method changes requiring new validation that provides better or equivalent results" **alternatively**: "Minor changes of the analytical method already covered by the IMPD for which no additional validation is necessary" to be replaced by: "Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided 1) the acceptance criteria are similar or tighter 2) the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results. The sentence "Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results" should be deleted accordingly. • Addition: Introduction of new RS, provided equivalence has been established to the previous RS.	<u>Proposed changes under SM:</u> • REJECTED: this example is covered by the 3rd bullet point • ACCEPTED • ACCEPTED <u>Proposed changes under NSM:</u> • ACCEPTED: the initial wording has been replaced by the alternative proposal to be in line with the BWP guideline • ACCEPTED: new row for reference standard changes has been created

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1271	1	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" 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	Proposed change: PARTIALLY ACCEPTED: reference to the shelf-life has been deleted, since the section is about Retest period of drug substance. The rest has been rejected since this information is already listed in the guideline in the stability section and is redundant. „Extension of retest period based on the currently approved stability protocol or scheme" In order to harmonize the list of examples, analogous change has been made in the SM: „Extension of retest period not based on the currently approved stability protocol or without prior commitment"
1271	3	Comments/Rationales: • 1st bullet point under SM: A restriction of storage conditions would be substantial only if due to safety concern. Otherwise, it corresponds to a tighter control of the product and should be considered as non-substantial. • 2nd bullet point under SM and 1st bullet point under NSM: The reference to the initial submission is proposed to be re-phrased. • 3rd bullet point under SM: The change "Extension of protocol duration …" could be classified as non-substantial modification (possibly under Art.81.9), since the stability	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		criteria (storage conditions, tests and acceptance criteria) for retest period do not change; the appropriate stability of the material will still be demonstrated over the extended protocol duration, and any significant trends which may lead to an OOS result during the retest period will be appropriately investigated. • Supporting stability data should allow for non-substantial changes e.g., to storage conditions or container closure. Proposed changes under SM: • 1st bullet point: Reduction of retest period due to safety concern and/or restriction of the storage conditions due to safety concern • 2nd bullet point: Extension of retest period ~~not based on a scheme approved within the initial submission~~ outside the agreed stability criteria (storage conditions, tests and acceptance criteria) or without prior commitment. • Move "Extension of protocol duration through additional timepoints to extend retest period" to Art. 81.9 NSM or NSM Proposed change/addition under NSM: • Extension of retest period based on the ~~scheme approved within the initial submission~~ agreed stability criteria (storage conditions, tests and acceptance criteria) • Addition: Additional intermediate stability timepoint (e.g., additional pull point at 42 months) without changing the conditions for the extrapolation, leading to corresponding interim shelf-life extension (Rationale: align with q-guideline for biologicals)	Proposed changes under SM: • PARTIALLY ACCEPTED: the wording has been revised to include both safety and quality reasons "Reduction of retest period and/or restriction of the storage conditions due to safety *and/or quality* concern." • NOT APPLICABLE – this example has been revised (see comment 1 to line 1271) • REJECTED: in line with the BWP guideline Proposed changes under NSM: • NOT APPLICABLE – this example has been revised (see comment 1 to line 1271) • PARTIALLY ACCEPTED: reference to the shelf-life has been deleted, since the section is about Retest period of drug substance.
1271	4	Comment: We consider that the requirement that 'extension of protocol duration through additional timepoints' need not be considered as a substantial amendment, assuming other factors, e.g., drug substance specifications and the principles of the retest period extension, are unchanged.	REJECTED – in line with the BWP guideline
1271	5	Comment: Addition for clarity	ACCEPTED

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Extension of stability protocol duration through additional timepoints to extend retest period	
1272	1	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"	REJECTED: Not applicable in this case. Examples from the BWP guideline are more generic compared to the guideline for chemicals. Using the same examples as per biologicals may be too restrictive for the IMPs of chemical origin.
1272	3	Comment/Rationale: • No mention is made of additional tablet strengths as an example, it should be included with the category of change, assume substantial modification required • A change of imprint / embossing does not have a functional impact to the product • Consider adding a functional score in the formulation • The change or removal of colorants (present at very low levels) in non-functional tablet coating do not have a functional impact to product. Proposed change under SM: • Consider including additional tablet strengths as SM Proposed additions under NSM: • Addition: Change of imprint / embossing / other markings provided it has no impact on blinding. • Addition: Change or removal of colorants in non-functional tablet coating	Proposed changes under SM: • PARTIALLY ACCEPTED: The example should not be restricted to tablets, but it should be more or include other dosage forms. The following example has been added "*Change and/or addition of drug product strength.*" Proposed changes under NSM: • ACCEPTED • REJECTED: too specific, the table is not an exhaustive list of examples
1273	1	Comment: Suggest to align examples and verbiage between both guidelines for consistency reasons	ACCEPTED: the wording in both documents has been aligned

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Line 1273: examples/verbiage "guideline-requirements-chemical-pharmaceutical-quality-documentation" and Line 728: examples/verbiage "guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal"	
1273	3	Comment/Rationale: • *"Replacement or addition of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated"* is an example of an Art 81.9 change for P.2.1 drug substance manufacturers (line 1267). We propose to have this added as appropriate example of an Art 81.9 change for P.3.1 drug product manufacturers as well, since no impact on product quality is expected under the conditions described. • 2nd bullet point under SM: proposal to remove "safety reason" as the deletion of a GMP site would occur as result of a GMP non-compliance (that might lead to a safety issue) • Proposal to add immediate packaging sites as Art. 81.9 NSM or NSM as no significant impact on product quality or safety trial expected, given the low complexity of the manufacturing operations involved (see as comparison IA/IAIN category in the variation guideline for marketed products). Additionally, until HA approval of the modification a sponsor's clinical materials cannot be shipped. If HA approval is delayed for whatever reason, the supply chain could be interrupted posing risk to study, site or patient. Balancing this risk with the potential impact to quality and the corollary submission in commercial space (the Variations Guidance), an Article 81.9 submission is considered appropriate. • Proposal to add the same precision as in the biologic guideline regarding the "Addition or replacement of secondary packaging or labelling site with valid GMP status" but to be considered as non-substantial". Proposed change/addition under SM: • 2nd bullet point: Remove "safety reason" • Add "immediate" to packaging site	Proposed change under SM: • REJECTED: in line with the BWP guideline • REJECTED

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• Move "Addition of (immediate) packaging site" from SM to Art. 81.9 NSM Proposed additions under Art. 81.9 NSM: • Addition: Replacement or addition of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated • Addition: Preferred: Addition or replacement of an immediate packaging site. Alternative: Addition or replacement of an immediate packaging site for non-sterile products. Proposed addition under NSM: • Addition: Addition or replacement of secondary packaging or labelling site with valid GMP status'	• REJECTED: GMP compliance has to be checked for primary and secondary packaging sites Proposed additions under Art. 81.9 NSM: • REJECTED: GMP compliance has to be checked for any new QC testing site • REJECTED: see above • REJECTED: see above Proposed addition under NSM: • REJECTED: see above
1273	4	Comment: "Addition of manufacturing, packaging, or testing site" remains listed as an example of a substantial modification. By analogy to line 1267, we propose that replacement or addition of a testing or packaging site, could be considered for inclusion as an Article 81.9 non-substantial change. In the case of testing sites, the same provision of "the same analytical methods are used, and method transfer has been demonstrated" as proposed for drug substance in line 1267, could be used for drug product. As all such sites would require GMP certification and/or a QP declaration, we believe that there is low risk to the safety of trial subjects or on the reliability and robustness of the data generated in the clinical trial arising from such a change.	REJECTED: GMP compliance of all packaging and QC testing sites has to be checked.
1273	5	Comment: Addition of an alternate site of drug substance manufacture within one company with unchanged manufacturing process and specifications is proposed as a non-substantial change, but there is no category for the equivalent change for drug product. Proposed change (if any):	REJECTED: the manufacturing process of a drug product is not equivalent with a synthetic process of a drug substance. Additionally, GMP compliance should be checked.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Add "Addition of an alternate site of drug product manufacture within one company with unchanged manufacturing process and specifications" to the column under non-substantial changes	
1274	3	Comment/Rationale: • It is stated that "Addition/change of importing site" is considered as a Substantial change. However, the need to provide details on the site(s) responsible for import in the EEA is 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), point 7.2.14. • The QP keeps oversight on importation sites, and the QP certification site is listed in the application dossier • Manufacturing and Import Authorisation (MIA) is part of the Part 1 of the CTA. Different countries have different requirements for the MIA and its annexes. The CTR536/2014 Part 1 is however not country specific, hence the current MIA including import should be sufficient: Additionally, there is the need to provide a QP statement for EU GMP equivalence. Proposed change under SM: • Following the MAA requirements for CP the information should not be required in Section P.3.1. **Alternatively**: Addition/change of importing site that is also the QP certification site, and move this requirement to Art. 81.9 NSM Proposed change/addition under NSM: • Addition (if the alternative above will apply): Addition/change of importing site that is not the QP certification site (i.e., the QP certification site does not change) • Addition: "name or address change of the importation site without a geographical change"	Proposed change under SM: • PARTIALLY ACCEPTED: the list of examples has been revised and aligned with the BWP guideline and following example has been included under NSM. "*Addition or replacement of an importation site that is not a QP certification site, with a valid GMP status.*" Addition or replacement of QP certification site (including batch release under import) is a SM.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			Proposed changes under NSM: • PARTIALLY ACCEPTED: see above • REJECTED: in line with the BWP guideline. Additionally, new GMP documentation has to be checked
1275	3	Comment/Rationale: QPs are certified, listed in the MIA and overseen by inspectorates; a timely information of the MS without waiting for approval should be sufficient. Proposed change/addition under SM: • Move "Addition/change of batch release certification site (QP certification)" to Art. 81.9 NSM Proposed change/addition under NSM: • Addition: "Name or address change of the QP release site without a geographical change"	Proposed change under SM: • REJECTED: GMP compliance has to be checked Proposed change under NSM: • REJECTED: see comment 3 to line 1274
1276	3	Comment/Rationale: • 1st bullet point under SM: The addition of IPCs or their tightening is not critical to the process but usually supporting consistent manufacturing. These changes often occur in small steps and should not require approval under a SM. • 2nd bullet point under SM: Please define "large scale up" (i.e., above or below 10 times with respect to the current batch size). Remove "limited" as it is more accurately defined as < 10-fold in text. • In case a process type has been established at the manufacturer for other products, scale-up can be seen as non-substantial (without significant impact on quality or safety). It would be recommended to indicate clearly in the initial IMPD that the process is claimed as standard by the manufacturer with appropriate justification.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• Suggest similar classification for fill-and finish processes as described in the Biologics guideline as scale-up might not always be substantial. <u>Proposed change under SM:</u> • 2nd bullet point: Scale-up for non-standard processes (e.g., lyophilization, aseptic manufacturing) or for large scale-ups such as that the multiplication factor for the scale-up exceeds 10 for standard manufacturing processes <u>Proposed change/addition under NSM:</u> • 1st bullet point: Modifications of the process parameters (same process) where no effect on product quality is expected. • 2nd bullet point: "~~Limited~~ Scale-up ~~(i.e.~~ such as that the multiplication factor for the scale-up does not exceed 10~~)~~ for standard manufacturing processes or non-standard processes when there is significant prior experience at the manufacturer (e.g. aseptic process, process for modified release forms)." • Addition: Addition or tightening of IPC with no safety reason • Addition: Scale-Up of filling process if supported by appropriate media fills.	<u>Proposed change under SM</u>: • ACCEPTED <u>Proposed changes under NSM</u>: • ACCEPTED • PARTIALLY ACCEPTED: the following wording has been included "Scale-up such as that the multiplication factor for the scale-up does not exceed 10 for standard manufacturing processes." The rest of the proposal has been rejected as there is no definition of "significant prior experience of manufacturer" • REJECTED: the table is not an exhaustive list • REJECTED: the table is not an exhaustive list. Addition
1276	5	Comment: It would be helpful to include examples of changes in the manufacturing process for the drug product that would be considered non-substantial amendments, as are provided for drug substance in line 1268. Proposed change (if any): Modifications of the process parameters (same process, e.g. slight modifications in mixing speed)	REJECTED: The table in section 9 is not an exhaustive list and it is the Sponsor's responsibility to decide on a case-by-case basis. The sponsor should contact the Reporting Member State in case of doubt.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1277	3	Comment/Rationale: • More information regarding compendial excipients (i.e., how to manage update of specifications and methods in case a new European Pharmacopeia edition is published) would be appreciated. • Alignment with specification of DS and DP. Proposed change/additon under NSM: • Addition: Deletion or replacement of test(s) due to compendial change	Proposed change under NSM: • REJECTED: the example under SM specifically refers to changes in excipient specifications that may affect product performance, regardless of compliance with Ph. Eur. Specifications for compendial excipients are not in general submitted in the IMPD.
1278	3	Comment/Rationale: • Wording is "New test method (e.g., NIR instead of HPLC)" but the 'instead' reads like a replacement of an existing test. With this rational, an actually "new" test would not be identified as a substantial change. Perhaps "Different test" might be clearer. • 2nd bullet point under NSM: It is not clear how there would be an update in the test procedure to comply with Ph Eur, USP or JP monograph if the excipients are non-pharmacopoeial? Please clarify. Proposed change/additon under SM: • Change: New or different test method (e.g., NIR instead of HPLC) or method changes requiring new validation.	Proposed change under SM: • ACCEPTED Regarding the comment on the 2nd bullet point under NSM the wording has been revised as follows to clarify that the comment refers to the method and not to the excipient monograph: " Update of the test procedure to comply with Ph.Eur., USP, or JP "

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1279	3	Comment/Rationale: • 1st bullet point under SM: Change the term "Extension" to "Widening" for consistency within and among other guidelines • 1st bullet point under SM: It is stated that the "Extension of acceptance criteria with clinical relevance" is considered a Substantial change. Clarification would be helpful on when a test has clinical relevance. • 1st bullet point under SM: The addition or expansion of an acceptance criterion to the existing spec should be a NSM if within the same test and no safety reason (see also comment under line 1269). • Addition proposed under SM to cover the addition of tests **with** safety/quality reason • For alignment with specification of DS and of excipient "Deletion or replacement of test(s) due to compendial change" is proposed to be added as Art. 81.9 NSM. • Replacement of a test of a parameter that has been demonstrated not to be critical and/or stability indicating is proposed to be added as NSM. • Consider under NSM removing "control of mutagenic impurities excluded" as the general text refers to addition of tests for non-safety related reasons. The addition of mutagenic impurity testing would constitute a case of addition of a test for a safety reason. Proposed change/addition under SM: • 1st bullet point: ~~Extension~~ Widening of acceptance criteria … • Addition of test(s) for safety/quality reasons, e.g., addition of mutagenic impurity control Proposed addition under Art. 81.9 NSM: • Addition: Deletion or replacement of test(s) due to compendial change Proposed change/addition under NSM:	Proposed changes under SM: • ACCEPTED • PARTIALLY ACCEPTED: the following wording has been used "*Addition of specification parameter(s) with clinical relevance or for quality/safety reasons (e.g., to control polymorphs in the drug product that have the potential to change during manufacture or on stability, to monitor unqualified*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• "Addition/replacement of test(s) (no safety reason~~, control of mutagenic impurities excluded~~)" • Addition: Additional acceptance criteria to existing test specification within same test with no safety reason • Addition: Change to the description/appearance of the dosage form as a result of a non-substantial change in the drug product shape/embossing and/or coating formulation.	*impurities , or to control mutagenic impurities)"* Proposed addition under Art. 81.9 NSM: • REJECTED: monographs for drug product are not so common and as this table is not an exhaustive list, this example has been rejected Proposed changes under NSM: • REJECTED • REJECTED: too specific • REJECETD: too specific
1279	5	Comment: We recommend adding a third point to the column of substantial changes to account for changes to the specification required for safety reasons Proposed change (if any): Add "Addition of tests for safety reasons (e.g. to monitor unqualified impurities or to control polymorphs in the drug product that have the potential to change during manufacture or on stability)".	PARTIALLY ACCEPTED: the following wording has been included "Addition of *specification parameter(s) with clinical relevance* or for *quality*/safety reasons (e.g. to control polymorphs in the drug product that have the potential to change during manufacture or on stability, *to monitor unqualified impurities or to control mutagenic impurities*)"
1280	1	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:	REJECTED: Replacement of the term "container" with "immediate package" is not acceptable as "container" is used within the CTD section Container closure system. Changes to secondary packaging are generally not critical and information on

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• 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.	supplier of packaging components is not part of the initial IMPD. Therefore, the proposal is rejected.
1280	3	Comment/Rationale: • Reference to change from one blister material to another which provides equivalent protections is not considered as warranting specific oversight and this change should be considered as non-substantial and not under Art. 81.9. The proposed CTIS (Clinical Trials Information System) summary data forms do not include details of specific packaging materials. Additionally, for DS non-substantial modifications would not require to be notified under Art.81.9 NSM. • Clarification needed for the classification of changes affecting other dosage forms not mentioned in the table of changes. It is suggested to widen the scope of the description to other pharmaceutical forms. Proposed change under Art. 81.9 NSM and under NSM: • Move "Change or new container closure system for solid oral dosage forms which provides equivalent or better protection (e.g., blister to blister)" to NSM • Change or new container closure system for e.g., solid oral dosage forms which provides equivalent or better protection (e.g., blister to blister, e.g., plastic to glass container for liquid products)	Proposed changes under Art. Á1.9 and under NSM: • NOT APPLICABLE – the example has been deleted because it was too confusing • NOT APPLICABLE – the example has been deleted because it was too confusing
1280	5	Comment: The reference to a diluted product does not seem correct in context. Proposed change (if any): New container closure system is introduced (e.g., less protective material, different container/material for liquid product)	ACCEPTED

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1280	5	Comment: The example "blister to blister" given for the Art 81.6 amendment is not particularly helpful. Proposed change (if any): Change or new container closure system for solid oral dosage forms which provides equivalent or better protection (e.g. blister with Tyvek lidding to blister with foil lidding)	NOT APPLICABLE – the example has been deleted because it was too confusing
1280	5	Comment: Examples of non-substantial amendments to the container closure system might include additional bottle sizes. Proposed change (if any): Add "Addition of a new size of the existing container closure system" under non-substantial amendment	REJECTED: this type of change could be considered a SM in specific cases. Additionally, the table is not an exhaustive list of examples.
1281	3	<u>Comment/Rationale:</u> • 1st bullet point under SM: Clarification needed about how to present the changes with respect to the device constituents' 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.). To make it clearer and to harmonise wording with new EMA guideline on "Quality documentation for medicinal products when used with a medical device" it is proposed to modify like "Medical device **or device part**" • 1st bullet points under SM and NSM: "Change to use a different medical device" and "changes to a medical device registered in the IMPD which is not considered to impact on the quality, safety and/or efficacy" may be contradictory causing confusion in classification. In former case change to a different device is simply a SM, while in latter case it also can be NSM. A change of wording is therefore proposed to "Add or change to a new or different medical device". • 2nd bullet point under SM: The term "registered in the IMPD" does not seem appropriate and is therefore proposed to be removed.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• 2nd bullet point under SM and 1st bullet point under NSM: In alignment with EMA Q&A Answer 2.6. of the June EMA Q&A document for devices & medicinal products, the addition of the intended purpose is proposed. • 2nd bullet point under SM and 1st bullet point under NSM: Please provide some examples of changes impacting the quality, safety and/or efficacy for medical devices, to support the evaluation. Proposed changes: • Suggest adding examples in the substantial and non-substantial categories (e.g., syringes, in-line filters, different finger plate or plunger rod etc.) • 1st bullet point under SM: "~~Change to use a~~ Add or change to a new or different medical device." • 2nd bullet point under SM: "Changes to a medical device or device part (design or intended purpose) ~~registered in the IMPD~~ approved within the initial submission if potentially impacting on the quality, safety and/or efficacy." • Under NSM: "Changes to a medical device or device part (design or intended purpose) ~~registered in the IMPD~~ approved within the initial submission which is not considered to impact on the quality, safety and/or efficacy."	Proposed changes: • REJECTED: in line with the BWP guideline. • PARTIALLY ACCEPTED: • REJECTED: change to a device part would mean a change to a medical device. The comment on "registered in the IMPD" has been accepted • REJECTED: change to a device part would mean a change to a medical device. The comment on "registered in the IMPD" has been accepted
1282	1	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-documentation-concerning-biological-investigational-medicinal" Proposed change: • Reduction in Shelf-Life if not safety or quality related	Proposed changes:

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome

		• 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
			• REJECTED: this example is indirectly covered by the 1st bullet point under SM
			• PARTIALLY ACCEPTED: the following wording has been used
			"Extension of shelf-life *based on the currently approved stability protocol or scheme.*"
			The shelf-life extension scheme is already described in the corresponding section of the guideline and this information is considered redundant and was not included.

1282	3	<u>Comment/Rationale:</u> • 1st bullet point under SM: Align with drug substance language (see line 1271) and relevant change descriptions in the biologics guideline. • Shelf-life reduction without quality or safety concerns shall not be considered as substantial change. Similarly, this is also listed in the respective guideline for the Biologics, where this wording is in the non-substantial column. • Re 2nd bullet point under SM: Should not be limited to the initial filing of the IMPD, as also an extension of the stability protocol can be approved as substantial modification (see 3rd bullet point). • 3rd bullet point under SM: The change "Extension of protocol duration …" could be classified as non-substantial modification (possibly under Art.81.9), since the stability criteria (storage conditions, tests and acceptance criteria) for shelf life extension do not change; the appropriate stability of the product will still be demonstrated over the extended protocol duration, and any significant trends which may lead to an OOS result during the retest period will be appropriately investigated.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• 3rd bullet point under SM: Extension of stability protocol duration through additional timepoints: it seems that this modification could be considered non substantial provided that the requirements listed in 2.2.1.P.8 are fulfilled and that the DP specifications are unchanged, especially due to the "statement that in case of any significant negative trend the Sponsor will inform the competent authority should be provided" (line 685-686) which all together ensure that there is no increased safety risk to trial participants. Consideration could also be given to aligning with the proposed draft Guideline EMA/CHMP/BWP/534898/2008 rev 2 line 735 which allows for inclusion of an additional intermediate stability timepoint which is not yet covered as a non-substantial modification. Proposed change under SM: • 1st bullet point: Reduction of shelf-life and/or restriction of the storage conditions due to safety or stability concerns. • 2nd bullet point: "Extension of shelf life - proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing clinical trial ~~has not been submitted/approved with the initial filing of the IMPD~~ (storage conditions, tests and acceptance criteria), when not previously agreed or without prior commitment." • 3rd bullet point: Move "Extension of stability protocol duration through additional timepoints to extend shelf life" to Art. 81.9 NSM. Proposed change/addition under Art. 81.9 NSM: • Addition (move from SM to art. 81.9 NSM): Extension of stability protocol duration through additional timepoints to extend shelf life Proposed change/addition under NSM: • Addition: Reduction in Shelf-Life if not safety or quality related.	Proposed change under SM: • ACCEPTED • NOT APPLICABLE: the wording has been revised in line with the BWP guideline • REJECTED: in line with the BWP guideline Proposed addition under Art. 81.9 NSM: • REJECTED: see above Proposed changes under NSM: • REJECTED: this example is indirectly covered by the 1st bullet point under SM • ACCEPTED

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		• Addition: "Additional intermediate stability timepoint (e.g., additional pull point at 42 months) without changing the conditions for the extrapolation, leading to corresponding interim shelf-life extension".	
To be added	3	Comment/Rationale: Please provide criteria to decide whether text change on the labels on immediate packaging & secondary packaging would classify as substantial or non-substantial, e.g., -> Substantial Modifications: - changes with potential impact on patient safety, e.g., new dosing instructions, route of administration - changes with potential impact on product quality, e.g., change of storage conditions -> Non-Substantial Modifications: - editorial changes without potential impact on patient safety or product quality - correction of typos - state something more precisely, e.g., change from "protect from light" to "store in outer carton to protect from light"	REJECTED: labelling is not covered by this guideline