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

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA  |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
|  | 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.  |  |
|  | ***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 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.  |  |
|  | 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. |  |
|  | The proposed revisions in section 9. are appreciated as giving more concrete guidance on classification of changes. |  |

1. Specific comments on text

| Line number(s) of the relevant text*(e.g. Lines 20-23)* | Stakeholder number*(To be completed by the Agency)* | Comment and rationale; proposed changes*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome*(To be completed by the Agency)* |
| --- | --- | --- | --- |
| 264-269 |  | 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. |  |
| 271-274 |  | 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.

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 |  |
| 446 |  | 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 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 |  | 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. |  |
| 523-524 |  | 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.’ |  |
| 675 |  | 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 |  |
| 713 -720 |  | 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. 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. |  |
| 1074 |  | 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. |  |
| 1186 |  | Comment/Rationale:Please make sure that chapter 9 is in line with the corresponding guidelines on biologicalsProposed change:Align the two guidelines. |  |
| 1189-1191 |  | 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” |  |
| 1215 |  | Comment/Rationale:Further clarifications on the difference between an 81.9 NSM and a NSM would be appreciatedProposed change:Please consider to provide more clarification. |  |
| 1229 |  | 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*Proposed change:Please consider providing more guidance on this matter. |  |
| 1236 |  | Comment/Rationale: Further clarification whether and if so, how a single change according to 81.9 should be submitted.Proposed change:Provide clarification |  |
| 1236-1245 |  | 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.
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| 1236-1245 |  | 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. |  |
| 1244-1245 |  | 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. |  |
| 1251 to 1252 |  | 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 … |  |
| 1256 |  | Comment/Rationale:Provide clarificationProposed change:Add a wording to clarify that this notification is not related to the type of change (i.e., SM or NSM) |  |
| 1258 |  | 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 RA and EC approval.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. |  |
| Column headline above line 1266 |  | Comment/Rationale:Please ensure that the headlines are harmonised between the two guidelines.Proposed change:Use the same terms as in the table headline of the guideline for biological IMPs |  |
| 1266 |  | 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 |  |
| 1267 |  | 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
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| 1268 |  | Comments/Rationales under SM:* 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.

Proposed changes/additions under SM:* 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

Comments/Rationales on NSM:* 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.
* 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
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| 1269 |  | 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.
* 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
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| 1270 |  | Comment/Rationale:* 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.
* 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.

Proposed changes/additions under SM:* 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

Proposed changes/additions under NSM:* “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 tighter2) 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.
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| 1271 |  | 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 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)
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| 1272 |  | 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
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| 1273 |  | 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
* 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’
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| 1274 |  | 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”
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| 1275 |  | 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”
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| 1276 |  | 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.
* Suggest similar classification for fill-and finish processes as described in the Biologics guideline as scale-up might not always be substantial.

Proposed change under SM:* 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

Proposed change/addition under NSM:* 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.
 |  |
| 1277 |  | 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
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| 1278 |  | 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.
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| 1279 |  | 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:* “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.
 |  |
| 1280 |  | 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)
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| 1281 |  | Comment/Rationale:* 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.
* 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.”
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| 1282 |  | Comment/Rationale:* 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.
* 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.
	+ 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 |  | 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"Proposed change: |  |

Please add more rows if needed.