20 September 2017
EMA/CHMP/QWP/546045/2017

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/834816/2015)

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	APIC
3	Astellas Pharma Europe B.V.
4	CureVac AG, Tübingen, Germany
5	EFPIA
6	Gilead Sciences International Ltd
7	LEO Pharma A/S
8	PIERRE FABRE MEDICAMENT
9	Quotient Clinical Ltd

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1.	The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually. ACRO welcomes and supports the draft guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials. In particular, ACRO supports the following underlying principles of the draft guideline: • The risk-based approach to documentation requirements focused on risk aspects of the investigational medicinal product, taking into account the nature of the product, the state of development/clinical phase, patient population, nature and	

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	severity of the indication and the characteristics of the proposed clinical trial. • The recognition that, as a consequence, it is not possible to define detailed requirements applicable to all different sorts of products and therefore that there must be flexibility in the documentation requirements, proportionate to the potential risk. • The emphasis on presentation of data in the form of succinct tabulated summaries, accompanied by an evaluation and justification, where appropriate, rather than a detailed description of studies and results. • The application of the same documentation requirements to both investigational medicinal products and auxiliary medicinal products, given that all medicinal products administered during a clinical trial should meet appropriate quality standards.	
1.	ACRO thanks the Agency for the opportunity to comment on this 'Draft Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials ' (EMA/CHMP/QWP/834816/2015). Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions at all.	
2.	On a positive note; • Overall excellent document which is giving a clear direction how IMPD's need to be written. o Clear different approach for IMPD versus marketing authorization applications o No detailed information is required, only key information to	Accelerated stability assessment program can be taken as supportive only. Stability studies in line with the ICH requirements are preferred, also for early development phases. No information on ASAP will be implemented into the

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	be given (appropriate level of detail we believe) o Science driven o Linked to safety and efficacy of the product o Special formulations are requiring more information o Based on the state of development (less for phase 1, more for phase 2 based on status of development) **1 main remark** • NO ASAP (accelerated stability assessment program) approach discussed in the stability section, more ICH driven (accelerated and long term stability). Ability to leverage ASAP approach is a key opportunity in early phases.	guideline. Proposed change is not accepted.
5.	EFPIA welcome the opportunity to review and comment on the revised guideline; the majority of the comments provided are focussed on the new text that has been included within this update. Information and discussion pertaining to impurities, the control strategy and the supporting justification of the specification are closely interlinked and as such prescriptive expectations as to where this information should be located within the quality documentation is not always helpful. The ability to utilise a combination of sections S3.2, S4.1, S4.5, P5.1, P5.5 and P5.6 and others as appropriate to demonstrate the process understanding and control strategy to avoid duplication would be welcome. Justification of the specification should be based on the available safety information and not historical batch data. EFPIA is concerned with the detail being requested for manufacture of the API starting materials in the clinical phase. The information	Q and A which are now published on the EMA website are related to Directive 2001/20/EC requirements. Some of them are also implemented in this document. Furthermore, it was announced that new Q and A will be created by the EC for new Regulation.

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	and knowledge available for materials used in the manufacture of the drug substance may be limited at early stages of development. Furthermore, development of the synthetic process will likely lead to changes in the route of synthesis. EFPIA has concerns that this requirement will restrict the ability of applicants to improve routes of synthesis and that the inclusion of such information in Section S2.3 will also lead to the need for more frequent and complex amendments. EFPIA believes that provision of such information should be restricted to submissions for phase 3 and beyond and that such details would be best included for information only in (e.g. in Section S2.6.) There are significant concerns with the proposed changes on drug substance stability. The need to provide site specific stability data to support the re-test period is considered beyond the requirements for a MAA and would pose undue burden for sponsors and introduce a delay in conducting clinical trials. Stability data should be provided for representative batch(es) and not necessarily for batches made by the specific process or at the specific site or scale. EFPIA has concerns regarding the significant changes to the drug product stability section and the conditions that are stated in order to extrapolate the shelf life. It is useful that the text allows some flexibility from the positions on extrapolation of stability data outlined in ICH Q1E. However, allowing a four-fold extrapolation is not consistent with a science and risk based approach to stability studies. Alternative approaches to evaluating drug substance and drug product stability (e.g. using an accelerated stability assessment program to model the degradation according to the	

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	modified Arrhenius law – also referred to as ASAP modelling) can allow for extrapolation beyond an arbitrary 4x fold extension and beyond an extrapolation of X+12 months. As such the shelf life assigned should be based on the understanding of the stability of the product provided by the applicant. Depending on the data available an extrapolation of real time data may be acceptable but should be justified (e.g. use of statistical plots, modelling and prediction tools, etc) Reference to the suitability of compendia is noted throughout the guideline. The requirement to demonstrate suitability of a monograph may be too strict for an early phase clinical or an exploratory trial; consideration should be given to the phase of development. Further clarity on how to demonstrate the suitability of a referenced monograph would be beneficial In the concept paper the EMA indicated that the revised guideline would incorporate the current set of Q&A's that are available, please confirm if these have been fully incorporated and thus these Q&A's will be withdrawn.	
7.	LEO Pharma A/S (hereafter referred to as LEO) welcomes the opportunity to give input to this draft guidance document. We respectfully submit the detailed comments below, for your consideration.	
9.	Comment: Post implementation of the Clinical Trial Regulation there is concern that following harmonisation of the guideline and Investigational Medicinal Product Dossier (IMPD) requirements across the European	

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	Union (EU), standards will become less flexible, with reduced potential for risk-based decision making within the development lifecycle. This is particularly of concern to the Phase 1 environment where there is some precedence for minor flexibility in terms of inclusion of certain information, e.g. validation of analytical procedures (2.2.1.P.5.3) and stability (2.2.1.P.8), as appropriate to the stage of development. It is welcome that the updated guideline continues to support this flexibility, to facilitate Phase 1 trial timelines and to maintain the EU as an attractive environment for Phase 1 clinical research for the global pharma and biotech industries.	

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
38 - 40	4.	Comment: The numbering of sections 2.1.S.3, 2.1.S.3.1 and 2.1.S.3.2 is inverted to “1.2.S” Proposed change (if any): We suggest to correct the numbering in these 3 lines to be consistent with the remaining sections.	Typo error, numbering was corrected. Proposed change was accepted.
199 - 201	1.	Comment: Regulation (EU) No. 536/2014 came into force on 20 June 2014 but, as currently estimated by the EMA, will not take effect until October 2018. The guideline should therefore clarify whether it will be effective only from the effective date of the Regulation or will replace current guidance issued with respect to current legislation (Directive 2001/20/EC), while recognising that some of the terminology used (e.g., auxiliary medicinal product) is specific to the Regulation and not referenced in the Directive. Proposed change (if any): Clarify whether the guideline will be effective only from the effective date of the Regulation or will replace current guidance issued with respect to current legislation (Directive 2001/20/EC).	This guideline will be effective from the effective date of the Regulation. During the transitional period, which is defined in the Regulation (EU) No. 536/2014, Sponsor could decide whether to follow Directive 2001/20/EC and the currently valid guideline CHMP/QWP/185401/2004 final or new Regulation and this guideline. No further clarification is required. Proposed change not endorsed.
206	1.	Comment: There is a typo (additional Space after the word	Accepted, Typo error was corrected.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"of-") in "state-of- the-art" Proposed change: "state-of-the-art"	
214-218	5.	Comment: It would be helpful to get guidance for cases when a synthetic active material (e.g. chemically defined drug substances, synthetic peptides, synthetic oligonucleotides) is chemically bound directly or via another linker molecule to a protein and polypeptide deriving from a recombinant or non-recombinant cell-culture expression system: which guideline should be applied: EMA/CHMP/QWP/834816/2015 ("chemicals") or EMA/CHMP/BWP/534898/2008 ("biologics")?	In case chemical material is bound to a biological/biotechnological material, the final molecule should comply with the "biologics" guideline for IMPs. Reference to other guidelines is not preferred because change in one guideline can cause problem in the other. No problems have been indicated in this area up to now, therefore no changes were made.
215 - 218	5.	Comment: The wording should be updated to include applicability of DS requirements to conjugates used in drug/biologic combination products. "…Auxiliary Medicinal Products containing chemically defined drug substances, synthetic peptides, synthetic oligonucleotides, herbal substances, herbal preparations and chemically defined radio-active/radio-labelled substances to be submitted to the competent authority for approval prior to beginning a clinical trial in humans Proposed change: **Relevant portions of this guidance also apply to products where the aforementioned drug substances are components (e.g. a synthetic peptide**	No change in this part is needed. In most cases where synthetic molecules are conjugated to any biological/biotech components, requirements defined in "chemical" IMP guideline are applied to material obtained by chemical synthesis and requirements included in "biological" IMP guideline are applied to the conjugates. Proposed change not accepted.

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		used in a protein-peptide conjugate). EMA/CHMP/RWP/534898 should be referred to for biological/biotechnology derived substances."	
215	5.	Comment: Auxiliary Medicinal Products is a new term under the clinical trial regulation, it would be helpful to provide a reference to the guideline *"Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)"* for clarity	This term is explained in the Regulation (EU) No 536/2014 and also in this guideline, no reference to another document is needed. Proposed change is not accepted.
236 - 238	4.	Comment: The Commission Regulation 536/2014 states under section G […] "*Quality data* 40. Quality data shall be submitted in a logical structure such as that of Module 3 of the ICH Common Technical Document format." Numbering of an IMPD according to this guideline is preceded by "2.1.", whereas Module 3 uses "3.2." as a prefix to the quality sections. Proposed change (if any): We suggest that it is clarified whether a specific numbering should be used to be compliant with the regulation and the	Regulation (EU) 536/2014 states an example of a logical structure – Module 3. Historically, numbering in the IMPD has been "2.1" therefore this guideline continues in this numbering. But in case Application with numbering used in Module 3 will be submitted, this will not be commented and it will be accepted. No further clarification is needed, proposed change is not endorsed.

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		guideline.	
237	5.	Comment: The provision of an IMPD in a clearly structured format following a numbering system consistent with ICH M4 format is recommended	Numbering in this guideline is patterned on the ICH M4 (CTD format)
242-244	5.	Comment: Consider including reference to USP monograph for active substance. In line 242, it is recommended to revise the wording to the following to ensure that a compendial reference can be made for a drug substance or IMP Proposed change: "For **drug substances** or IMPs to be used in clinical trials as described in chapters 2 to 8, reference to either European Pharmacopoeia (Ph. Eur), the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) is acceptable."	Proposed change is accepted.
258-259	6.	Comment: Clarify 'the principles of the methods used' Proposed change (if any):	This was also in the previous guideline, there was no problem with understanding what does "the principles of the methods used" mean. No further clarification is needed.
263-267 883-837	9.	Comment: We propose that further clarification is provided regarding how the Active Substance Master File (ASMF) can be referred to for the purposes of a clinical trial application (CTA). It is our understanding that reference to an ASMF can only be made for a CTA if the ASMF has been reviewed by a Competent Authority as part of a Marketing Authorisation.	ASMF can be used without it has been reviewed by the Competent authority as part of a Marketing Authorisation. Both guidelines refer to Marketing Authorisations only, but the same procedure can be used for clinical trials. Proposed change not supported, one sentence for clarification was added.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): From Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in their current version should be followed. To Reference to an Active Substance Master File (that has been reviewed by a Competent Authority as part of a Marketing Authorisation) or a Certificate of Suitability of the European Directorate for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in their current version should be followed.	
264-266 and 834-837	5.	Comment: The ASMF Guideline and the described procedure (including Letter of Access and Submission Letter) do not contain	ASMF can be used without it has been reviewed by the Competent authority as part of a Marketing Authorisation. Both guidelines refer to Marketing Authorisations only, but the

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		information for the submission of ASMF in the context of clinical trial applications. Guidance is needed how to apply the guideline to clinical trial applications. Guidance should be provided, whether information other than the applicants part of the ASMF (such as specifications, analytical methods, analytical validation of the sponsor) are needed.	same procedure can be used for clinical trials. One sentence for clarification was added.
277	5.	Comment: Suggest that proposed INNs are not included. INNs may change during the process, which could result in confusion. Either delete reference to INN, or include only if approved. Proposed change: Information concerning the nomenclature of the drug substance (e.g. ~~proposed INN-name~~, pharmacopoeial name,... OR Information concerning the nomenclature of the drug substance (e.g. ~~proposed INN-name~~, **INN (if approved),** pharmacopoeial name,...	Change is accepted (INN (if approved)
297	1.	Comment: There is a typo (additional Space after the word “radio”) in “radio -labelling”	Accepted, Typo error was corrected.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: "radio-labelling"	
316-317	5.	Comment: As currently written the added text could be interpreted to include irradiation and production of radioactive materials in a nuclear reactor, which we don't believe is the intent. Clarification to the text is suggested to make sure the intent is clear. Proposed change: "…as well as the source of any **cyclotron** irradiation target materials and **production** site(s) at which irradiation occurs."	Proposed change is accepted.
321	1.	Comment: There is a typo (additional Space and ".") in between two sentences: "…should be provided. . Any relevant…" Proposed change: "…should be provided. Any relevant…"	Accepted, Typo error was corrected.
321	6.	Comment: Clarify 'Any relevant process controls' Proposed change (if any): Any process controls identified as critical should be indicated.	Relevant process controls are not always critical, but still should be indicated. Proposed change not endorsed.
322-323	5.	Comment: Information and discussion on the stereo-chemical properties of the starting material should be located in Section S2.3 not in S2.2. Proposed change: ~~The stereo-chemical properties of starting materials should be discussed, where applicable.~~	This information can be stated in both sections. Proposed change is not accepted.
322-323	6.	Comment: The sentence*: 'The stereo-chemical properties of*	Requirements on stereo-chemical properties of starting

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		starting materials should be discussed, where applicable' is better placed in the control of materials section. In the process description, you would at most "indicate" the stereo-chemical nature of the starting materials. This would not be discussed here. Proposed change (if any): It is suggested that this sentence is moved to 2.2.1.S.2.3	materials can be moved to "Control of materials" section. Proposed change accepted.
331	1.	Comment: The preferred term should not be "organic-chemical" but "organo-chemical" Proposed change (if any): "organo-chemical"	Accepted, term organic-chemical was corrected to organo-chemical.
337	5.	Comment: Batch size in development can vary; for clinical batches manufactured the batch size of each lot is included in Section S4.4 therefore this requirement could be removed from this section. Proposed change: ~~The production scale or range of batch sizes to be used in the clinical trial should be stated~~	Proposed change is accepted
337	6.	Comment: The production scale is expected to change significantly during development, possibly even during the same clinical study. Maintaining the accuracy of a scale statement is not practical or useful for the quality assessment. This sentence should be deleted. The batch history section can capture the manufacturing scale of previous batches. Proposed change (if any): The batch history section can	Proposed change is accepted, the sentence was deleted.

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		capture the manufacturing scale of previous batches.	
339-343	5.	EFPIA is concerned with the detail being requested for manufacture of the API starting materials in the clinical phase. The information and knowledge available for materials used in the manufacture of the drug substance will be limited at early stages of development. Furthermore, development of the synthetic process will likely lead to changes in the route of synthesis. EFPIA has concerns that this requirement will restrict the ability of applicants to improve routes of synthesis and that the inclusion of such information in Section S2.3 will also lead to the need for more frequent and complex amendments. EFPIA believes that provision of such information should be restricted to submissions for phase 3 and beyond and that such details would be best included for information only in Section S2.6. Proposed Change: **From phase III , b**rief information on synthesis or flow chart of the starting material(s) should be provided unless otherwise justified **in Section S2.6, e.g., where starting materials are commercially available**.	Requirement on the synthesis or flow chart for starting materials was removed but requirements on sufficient process description was added to the "Description of manufacturing process" section that it is obvious how impurities are introduced in the process. Proposed change partly accepted.
343 - 344	3.	Comment: In the early development stage, the synthesis method and/or specification of starting materials might still be	Requirement on the synthesis or flow chart for starting materials was removed. Early development phase can be acceptable as justification for

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		under development. Can the following statement be the justification for the absence of starting material information, e.g., “Due to early development stage, the information is not yet available.”?	some missing data in general but it is pointed out that phase 3 cannot be taken as early development phase. Comment accepted.
343-344	6.	Comment: This new text should be either removed or clarified and limited. If we have to provide detail on the starting material synthesis it will make it difficult to maintain compliance with this aspect of the IMPD, as changes to the synthesis are inevitable. Proposed change (if any): It could be reworded to indicate that an exemplary synthesis should be provided. Or to say that this requirement only applies to Phase 3 trials.	Requirement on the synthesis or flow chart for starting materials was removed but requirements on sufficient process description was added to the “Description of manufacturing process” section that it is obvious how impurities are introduced in the process. Proposed change not accepted.
343-344	7.	Comment: As information on synthesis of starting materials is normally not available in early clinical stages, the starting material may even not be defined at that stage in development; it is suggested to delete this requirement, alternatively to restrict it to late phase development. Proposed change (if any): ~~*Brief information on synthesis or flow chart of the starting material(s) should be provided unless otherwise justified.*~~	Requirement on the synthesis or flow chart for starting materials was removed but requirements on sufficient process description was added to the “Description of manufacturing process” section that it is obvious how impurities are introduced in the process. Proposed change partly accepted.
343-344	9.	Comment: It would be helpful to provide an example of a justification for not providing brief information on synthesis or flow chart of a starting material(s), e.g. for a starting material (s) that	Requirement on the synthesis or flow chart for starting materials was removed but requirements on sufficient process description was added to the “Description of manufacturing process” section that it is obvious how impurities are

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		is commercially available. Proposed change (if any): From Brief information on synthesis or flow chart of the starting material(s) should be provided unless otherwise justified. To Brief information on synthesis or flow chart of the starting material(s) should be provided unless otherwise justified, e.g. the starting material(s) is commercially available.	introduced in the process. Proposed change partly accepted.
344	5.	Comment: As in Lines 316-317, clarification to the text is suggested to make sure the intent is clear. Proposed Change: "…as well as the source of any **cyclotron** irradiation target materials and **production** site(s) at which irradiation occurs."	Proposed change is accepted.
348 - 349	1.	Comment: ACRO concurs that information on process validation and/or evaluation is not applicable for a risk assessment of active substances intended for clinical trial use. Proposed change (if any):	No change proposed.
375	5.	Comment: reference to ICH M7 to be added. Proposed change: Discussion on (potential) mutagenic	Proposed change is accepted.

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		impurities **according to ICH M7**…	
377 877	9.	Comment: The stage of the manufacturing process in which the solvent/catalyst is used should be taken into account when providing a justification for the absence of routine control for solvents/catalysts. Proposed change (if any): From Absence of routine control for solvents/catalysts used in the manufacturing process should be justified. To Absence of routine control for solvents/catalysts used in the manufacturing process should be justified taking into consideration the stage of the manufacturing process in which the solvent/catalyst is used.	Current sentence is sufficient, because absence of routine control can be justified e.g. by the stage of process in which the reagent/solvent/catalyst is used. No further details are needed. Proposed change is not supported.
379-382	5.	Comment: Some radio-labelled substances are administered in very low doses (diluted with cold API) where the chemical purity may not be relevant from a toxicological perspective. Proposed change (if any): add "**(where relevant)**" after "chemical purity" in line 382.	Chemical purity is an important parameter. In some special cases (e.g. low doses) omission of this control can be justified. But it is not endorsed to implement the proposed change into the guideline.
389	5.	Comment: Specifications for peptides would typically include tests for quantity instead of assay. Where the	In this guideline general requirements are set, it is not possible to cover all the specific requirements for all types of

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		guidance says “Tests for identity and assay are mandatory”, please clarify if quantity is appropriate instead of assay for synthetic peptides. Proposed Change: “Tests for identity and assay **or quantity** are mandatory.”	drug substances. Furthermore, term “quantity” is not commonly used. Assay for peptides can be expressed by molecular weight or calculated but term assay is still used. Proposed change is not endorsed.
391-393	5.	Comment: The text as written does not differentiate requirements based on phase of development and that dose administered and the duration of study can be considered when establishing impurity acceptance criteria. Proposed change: **Impurity** limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies **and consideration of exposure**. A lower % level of an impurity in the non-clinical lot can qualify a raised % level in clinical lots based on higher dosing and exposure in the non-clinical studies. ICH requirements of e.g. Q3A and Q3B do not need to be met in the investigational phases of development, but, if met, no further justification is required. The justification of impurity limits should also take into account the dose and duration of the clinical study.	It is not needed to add further explanation into the guideline. Now there is written that in case ICH impurities limits are fulfilled, no further limit justification is needed. That means that in other cases justification of limits is responsibility of the Sponsor/Manufacturer and reference to early phase of development or dose/exposure duration can be used. Proposed change is not supported.
391-393	5.	Comment: ICH requirements for impurities do not apply to peptides. However, the European pharmacopeia includes thresholds for impurities in synthetic peptides. Please clarify the guidance to indicate appropriate approaches for impurities in synthetic peptides.	Proposed change is accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed Change: "The limits should be supported by the impurity profile of batches of the active substance used in non-clinical and clinical studies. If ICH **or European Pharmacopoeia** requirements are met, no further limit justification is expected."	
391-393	7.	Comment: As there are only few batches to base the limits for impurities on during development, it is suggested to change the text, so that the requirements to impurities as stated in Guideline ICH M7 could be applicable for all impurities during early development, and the above requirement is applicable only during late development, e.g. for phase III clinical studies. Proposed change (if any): *The limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies. If ICH requirements are not met, further limit justification will be expected.*	It is not requirement on compliance with ICH limits. There is written that in case ICH requirements on limits for impurities are met, no further justification is needed. This applies for all phases of development. Proposed change not supported.
419-420	6.	Comment: Suggest modifying the sentence *"The acceptance limits (e.g., acceptance limits for the determination of the content of impurities, where relevant)".* If this is referring to impurity acceptance limits it is more correctly presented in the specification section. Proposed change (if any): Removal of this phrase.	This is referring to the acceptance limits of validation parameters, not to impurities acceptance limits. Proposed change not endorsed.
Lines 419-	5.	Comment: The suitability of the analytical methods used	Suggested wording is quite vague and would be difficult to

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423 And 589-593		should be confirmed. The acceptance limits (e.g., acceptance limits for the determination of content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in tabulated form. Proposed change: The suitability of the analytical methods used should be confirmed. ~~The acceptance limits (e.g., acceptance limits for the determination of content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in tabulated form~~. **At minimum, an overall description summarizing the method qualification information is sufficient for Phase I clinical trials.** Justification: Consistent with current practice and phase appropriate method validation.	interpret both for Sponsors and authorities. This wording is included in currently valid guideline and no problems have been identified for phase I clinical trials. Proposed change is not endorsed.
431-432	6.	Comment: If the only concern is to link specified unknown IMPs from one method to the next, then it should be worded as such (i.e., delete "especially"). If there are other concerns, then further definition is required for what a major change is. Proposed change (if any):	It is not the only concern to present cross-validation for unknown impurities defined by rrt, but it is one of the main concerns. There is no place in this guideline to strictly describe all the possibilities. Whether it is a major change or not, this should be justified by the Sponsor. Proposed change not endorsed, but requirement on cross-

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			validation was slightly softened.
431 - 433	3.	Comment: The amount of the sample of preclinical batch is typically limited. The overall development program of a medicinal product from preclinical stage to phase-3 studies sometimes takes long time and thus the preclinical batch may not be available for the re-analysis at a later development stage. Even if it is available, the quality of the preclinical batch may be deteriorated over the course of long storage period and may not be suitable for use of re-analysis. Considering that the purpose of the cross-validation is to confirm that the new method can produce comparable or improved results compared to the old one, the cross-validation can be conducted using a suitable sample (e.g. stressed sample or impurity-spiked sample) and not necessarily to be performed using the preclinical batch. We propose rewording the last sentence as following (delete strike-through and add underlined texts). Proposed change: *In case of major changes in analytical methods, cross-validation data should be presented especially for specified unknown impurities identified by their relative retention time (RRT), unless otherwise justified. ~~A re-analysis of preclinical batch with the new method should also be performed~~. A re-analysis may be necessary using a suitable sample, e.g.,*	Requirements on cross-validation and re-analysis of preclinical batch were softened. Proposed change is accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		stressed or impurity-spiked drug substance lot.	
431 - 433	5.	Comment: There is potential for confusion with regards to use of 'major change' vs 'substantial modifications' of analytical methods cited in Table 3 on page 38 of the draft guidance, it is suggested that the wording is amended to better correlate and that the need for cross-validation data and re-analysis of previous batches is limited to when a new test method is utilised. Proposed change: In case of ~~major~~ changes in analytical methods **that constitute a substantial amendment, e.g., change in test method type (see Table 3)**, cross-validation data should be presented especially for specified unknown impurities identified by their relative retention time (RRT).	The need to cross-validate the method is not only in case totally new analytical method is used. Also major changes in analytical conditions for e.g. HPLC can be made and cross-validation should be considered. Proposed change not accepted.
431-433	7.	Comment: It is acknowledged that older batches used for preclinical testing, and previously tested by the former version of the method, should be retested by the new version, in order to determine the impurities and their levels by the revised method, and compare these with the results of the former version. However, formal cross-validation of the two versions of the method seems superfluous. Proposed change (if any): *In case of major changes in analytical methods, ~~cross-~~comparison of data should be presented, especially for specified unknown impurities identified by their relative retention time (RRT). A re-*	Requirements on cross-validation and re-analysis of preclinical batch were softened. Proposed change is accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		analysis of preclinical batch with the new method should also be performed.	
432-433	5.	Comment: There are concerns regarding the requirement "A re-analysis of preclinical batch with the new method should also be performed." This should NOT be a requirement – for example if the original method and the new method are equivalent in their analysis of the impurities in the profile NO further testing should be needed. (Furthermore, a retest might confuse the picture as no longer reporting the levels of degradants that were present in the lot at the time of original test and used). Proposed change : "A re-analysis of preclinical batch with the new method should also be performed **unless otherwise justified**."	Requirement on re-analysis was too strict, it was reworded accordingly: A re-analysis of preclinical batch with the new method should also be considered, where relevant. Proposed change not used, but rewording was introduced.
432-433	6.	Comment: Generally, the reanalysis of nonclinical batches should not be required, and this sentence should be deleted: *"A re-analysis of 432 preclinical batch with the new method should also be performed."* If cross validation is performed and the methods are shown to be equivalent, then there is no reason to retest a preclinical batch. The only time where one would retest a batch is if the new method is able to separate additional impurities that the old method could not.	Requirement on re-testing of preclinical batch was quite strict. Modification is endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Replace the word 'performed' with 'considered' or Delete sentence	
435 - 441	1.	Comment: ACRO recommends adding guidance on the minimum number of batches on which analytical data should be provided to support each phase of clinical research. Proposed change (if any): Add guidance on the minimum number of batches on which analytical data should be provided to support each phase of clinical research.	Number of batches could differ for each type of drug substance and it is not possible to recommend any specific number of batches. Not accepted.
438	1.	Comment: There is a typo (additional Space between two words"): "If data are not" Proposed change: "If data are not"	Accepted, Typo error was corrected.
438 - 440	5.	**Proposed change**: 'If data are not available for the batches to be used in the current clinical trial, data for representative batches ~~**for each drug substance manufacturer**~~ may be submitted instead.' **Rationale**: the sponsor should have the knowledge and understanding to decide which batches are appropriate to submit in the batch analyses section as representative of the drug substance to be used in the clinical trial. Data may not be available from each potential drug substance manufacturer at the time of filing.	This is requirement from Q&A on EMA web site. It is important to see results for at least one representative batch from each drug substance manufacturer. In case there are no data from one manufacturing site justification can be provided that no material from this site will be used in the clinical trial and no batch analysis data will be required. In case drug substance from all manufacturing sites will be used for drug product manufacture, relevant data for at least one representative batch should be provided. Proposed change is not endorsed.
441	5.	Comment: Batch analyses data should be used to support the safety of	It is true that it is not essential to see previous/historical specifications, but is more important whether the batch

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
and 604 - 605		the product in the clinical study. The acceptance criteria can change over the development of a product and as the amount of batch data increases the inclusion of the 'current' acceptance criteria, as found in S.4.1/ P.5.1, can be misleading and often warrants clarification notes to explain historic batches were tested to a previous version of the specification. Please remove the expectation for inclusion of specification acceptance criteria in these sections. Proposed change (if any): The batch number, batch size, manufacturing site, manufacturing date, control methods, ~~acceptance criteria~~ and the test results should be listed.	conforms to current specification. Proposed change is accepted.
459	1.	Comment: More guidance should be provided here as some regulatory authorities routinely ask for sponsors to confirm that the components of the drug substance container closure system comply with applicable Ph.Eur monographs, EC Directives and EC Regulations. As examples, here are some blinded questions, from an assessor who reviewed an IMPD in 2015 to support a CTA for a Phase III study, to illustrate this point: *It should be confirmed that the plastic manufactured by XXXX meets Regulation (EC) 10/2011 and its amendments.* *The Applicant should confirm that the drug substance is packaged in a container closure system that meets the corresponding relevant standards in force (I. e. Directives,*	For clinical trials brief information on type of container and used material only is sufficient. No detailed information on quality of used materials is required. A sentence from drug product container closure system could be added (If non-compendial materials are used, a description and specifications should be provided.) Proposed change partly accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Eur. Ph. etc.). Proposed change (if any): Describe in more detail the information that is required on the drug substance packaging system.	
462 - 464	1.	Comment: The examples cited for 'representative' are collectively very prescriptive and don't allow for a scientific determination of what would be considered representative in relation to parameters with the potential to affect product quality. The requirement for site-specific stability batches goes beyond what is required for MAA. Currently, representative batches are acceptable from any site, provided the sponsor defends acceptability. Also a different site should not impact stability as long as the drug substance demonstrates the same physical and chemical properties. In early development, laboratory scale batches and/or pilot scale batches- produced with same composition and similar process- allow for the rapid detection of stability data out of trend and by extrapolating these data the ability to set an expiry for clinical batches compatible with running of global clinical trials Proposed change: "Stability data should be provided for batch(es) manufactured according to the representative process ~~(the same/very similar synthesis, the same manufacturing sites, comparable batch size)~~ and can be supported by data from batch(es) manufactured by previous	The requirement on stability data from each manufacturing sites is too strict and will be deleted from the guideline. Requirements on the same/very similar synthesis and comparable batch size will be kept in this section. Proposed change is partly accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		processes"	
462-464	8.	A "*representative process*" is defined in the guideline as a process with "*the same/very similar synthesis, the same manufacturing sites and comparable batch size*". We consider that stability data of a different manufacturing site can be used as supportive stability data if the synthesis is similar or very similar and if the batch size is comparable, whatever the manufacturing sites. Proposed change: "*Stability data should be provided for batch(es) manufactured according to the representative process (the same/very similar synthesis, ~~the same manufacturing sites~~, comparable batch size) and can be supported by data from batch(es) manufactured by previous processes*."	Proposed change accepted.
463-464	6.	Comment: Stability of the API is a property of the molecule, not of the manufacturing site. Suggest to remove the requirement of "the same manufacturing sites" and "comparable batch size". Otherwise this reads that we would have to have stability data on a scaleup batch before we could use the scaleup batch Proposed change (if any): Remove the requirement of "the same manufacturing sites" and "comparable batch size".	Scale up can be critical for synthesis, therefore requirement on comparable batch size is adequate. There is no requirement that each scale up should be supported by stability data. The requirement on the same manufacturing site is too strict, this requirement was deleted. Proposed change partly accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
466	6.	Comment: Photostability is generally performed late in clinical development, so timing for when this is done should be specified. Hygroscopicity should be included in the general information section 2.2.1.S.1, and not 2.2.1.S.7. Degradation pathways should be described in 2.2.1.S.3.2 or perhaps 2.2.1.S.2.6, and not 2.2.1.S.7. Proposed change (if any): Edit as in comments	Photostability and hygroscopicity are only examples of critical parameters, therefore change in wording is not endorsed. Degradation pathways are in IMPDs usually stated in Impurities or Stability section. It is no problem for Sponsor, to make reference to Impurities section, if applicable. Proposed changes are not supported.
469-471	5.	Comment: The possibility to extend the defined retest period by non-substantial amendment should be included. Proposed change: The retest period should be defined based on the available stability data and should be clearly stated. **The retest period may be extended without a substantial modification submission on the basis of additional data from stability studies defined in the IMPD.** In case no retest period is defined, statement should be included that the drug substance is tested immediately before the drug product manufacture.	Possibility of retest period extension without SM was added. Proposed change accepted.
469-471 922-925	9.	Comment: For active substances covered by a Certificate of Suitability (CEP) which does not include a retest date, it should be stated that supporting stability data and a retest period	Proposed change is accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		should be provided. Proposed change (if any): From The retest period should be defined based on the available stability data and should be clearly stated. In case no retest period is defined, statement should be included that the drug substance is tested immediately before the drug product manufacture. To The retest period should be defined based on the available stability data and should be clearly stated. For active substances covered by a Certificate of Suitability (CEP) which does not include a retest date, supporting stability data and a retest period should be provided. In case no retest period is defined, a statement should be included that the drug substance is tested immediately before the drug product manufacture.	
471	6.	Comment: Remove the word 'immediately' Proposed change (if any) Remove the word 'immediately'	Without submission of stability data, no retest period can be defined and drug substance has to be tested immediately before use. Without the word "immediately" the sentence makes no sense. Proposed change is not accepted.
473	1.	Comment: More guidance should be provided here	Proposal accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		regarding the pharmaceutical form for the drug product. Sponsors should be encouraged to use one of the standard terms in the EDQM Standard Terms database. For example, some sponsors often use the term 'solution for injection' in the IMPD to describe the IMP, which does not match the route of administration described in the clinical trial protocol where the IMP will be administered by intravenous infusion. Proposed change (if any): Encourage use of standard terminology from the EDQM Standard Terms database.	Addition of sentence: Standard terminology from the EDQM Standard Terms database should be preferably used for dosage forms, where applicable.
476-477 928- 929 1042-1044	5.	Comment: The quantitative composition of prefabricated components (e.g., capsule shells) and excipient mixtures (e.g., film coating mixtures) may be proprietary information. In these cases, providing the qualitative composition should be acceptable. Proposed Change: "~~This includes also~~ **In the case of proprietary** prefabricated components (e.g., capsule shells) and excipient mixtures (e.g., film coating mixtures)**, a qualitative composition is sufficient**"	Proposed change is accepted, information on qualitative composition is sufficient for proprietary components and mixtures.
476-L477	8.	"*The complete qualitative and quantitative composition of the IMP should be stated. This includes also prefabricated components (e.g. capsule shells) and excipient mixtures (e.g. film-coating mixtures).*" To avoid any different interpretation, it should be specified that flavours are not considered as excipient mixtures in this guideline. Complete information will be available for the	The same requirements apply both for coating material as well as flavour. Therefore it cannot be specified that flavours are not considered excipients mixture. Proposed change is not supported.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Marketing authorisation application file. Proposed change: "*The complete qualitative and quantitative composition of the IMP should be stated. This includes also prefabricated components (e.g. capsule shells) and excipient mixtures (e.g. film-coating mixtures). This does not include qualitative and quantitative composition of flavours.*"	
482		Comment: In the draft guideline it is stated: *"If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET)."* The value of this addition is questioned. Proposed change (if any): omit reference to the time zone requirement	The need for calibration time specification is stated in par. 2.2.1.P.8 – Stability, of the current guidelines ("For radiopharmaceuticals, the time of calibration should be specified, since the stability also depends on the half-life of the radioactive isotope"). Indeed, calibration time, also known as activity reference time, allows to properly calculate, based on the decay law, the activity of any radioactive compound at any time, which may be of concern in the evaluation of stability and other related parameters (e.g. radionuclidic impurities). In principle, it might happen that a long-lived radionuclide is purchased in a different country, with a time zone which is not the same as that of the country where the radionuclide is then used. It is our opinion that, in this case, time zone specification might help to minimize possible calculation errors. Proposed change not endorsed
487 - 488	3.	Comment: The statement sounds logical. However, the clarification is necessary here as to what information is expected from the	It is not possible to specify in such a detail, which justification is expected for every possibility. Suitable justification should be provided for. e.g. non-compendial excipient used, colorant

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		applicant. Is a statement from the applicant sufficient? Should we write a justification, also referring to the paediatric guideline (EMA/CHMP/QWP/805880/2012 Rev. 2)? Should we demonstrate the safety of e.g. devices (robustness, no loose parts?), or packaging materials (e.g. statement of suppliers of plastic bottles regarding absence of certain chemicals, leachables)?	or antimicrobial component, new dosage form… But in line with proposal send by EFPIA, paediatric population will be replaced by patients in general.
487 - 488	5.	Comment: It is not clear why this section specifically mentions paediatric studies. For clinical studies in any population the dosage form and the administration device if applicable should be safe and suitable for use. Proposed change (if any): if needed the text should be revised as follow: "~~For paediatric studies, t~~The medicinal product components, the dosage form and the administration device if any should be safe and suitable for the **patient** ~~paediatric~~ population."	Proposed change is accepted.
492	5.	Comment: Extemporaneous preparation is general understood as IMP manufacturing on clinical site, which is more than dilution or reconstitution. Proposed change For extemporaneously prepared medicinal products, the method of preparation should be summarised and reference made to a full description in the clinical protocol ***or associated handling instructions which will***	Proposed change is accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		be available at the clinical site.	
508	1.	Comment: ACRO recommends that the guideline should confirm whether or not the site where QP release is performed in the EEA should be included in this section of the IMPD. Proposed change (if any): Clarify whether or not the site where QP release is performed in the EEA should be included in this section of the IMPD.	Proposal accepted. One sentence has been added.
512 - 516	5.	Comment: Suggest alignment of terminology for packaging/ re-packaging and labelling/ re-labelling with the CTR Article 61 for consistency.	Terminology used in Article 61 is implemented into the guideline.
518	9.	Comment: Typically, we do not include batch formulae for early Phase drug substance in bottle or drug substance in capsule IMPs. The required amount of drug substance is filled individually into the container closure and, therefore, a batch formula is not considered to be required at this stage of development. Proposed change (if any): From The batch formula for the batch to be used for the clinical trial should be presented. To	This sentence is included in the current guideline, up to now no problems with this requirement has been recognised. For early phases of development, justification of missing information is common and is often accepted. Proposed change not supported.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The batch formula for the batch to be used for the clinical trial should be presented unless otherwise justified.	
527	1.	Comment: The plural “Controls” is inconsistent with the singular “Control” used for example in the equivalent guideline for biological investigational medicinal products (EMA/CHMP/BWP/534898/2008). Proposed change (if any): Ensure consistency across guidelines.	This comment is irrelevant to scientific background of this guideline. Proposed change not accepted.
527-535	9.	Comment It is unclear whether the text in lines 532-535 applies to Phase III clinical trials only or does it also apply to the non-exempt Phase I and Phase II trials, namely: non-standard manufacturing processes and manufacturing processes for sterile products. If not, what information is required for non-standard manufacturing processes and manufacturing processes for sterile products. Please can clarification be provided. Furthermore, it would be helpful to provide some examples of non-standard manufacturing processes.	This requirement is stated in current guideline. It is clear that text in lines 532-535 applies to Phase III clinical trials (it is included in the headings: Additional information for phase III clinical trials). The name of the whole section is “Controls of critical steps and intermediates”. Information on critical steps and intermediates should be provided for phase III studies always, and regardless of Phase of the study for non-standard manufacturing processes or manufacture of sterile products. It is not possible to provide any examples of non-standard manufacturing processes, because no exhaustive list is available and this could lead to further discussion whether other processes not included in the list are non-standard or standard. Proposed change is not supported, but requirements on controls of sterile manufacturing process are added.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
536 - 540	1.	Comment: While ACRO concurs that, in general, information on process validation and/or evaluation is not applicable for a risk assessment of finished products intended for clinical trial use, in the case of sterile products manufactured using aseptic processes, ACRO suggests including the recommendations provided in the guideline for biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs, in order to demonstrate the efficacy of aseptic processing operations. Proposed change (if any): In the case of sterile products manufactured using aseptic processes, include the recommendations provided in the guideline for biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs.	Proposed change accepted, recommendations from EMA/CHMP/BWP/534898/2008 are included in “Control of critical steps and intermediates” section.
537 - 540	5.	Comment: The requirement for the validation of ‘non-standard manufacturing processes’ is a significant constraint on innovation and should not be necessary. Validation is usually conducted prior to submission of an MAA but not for clinical trial purposes with the exception being sterilisation process. It is suggested that an appropriate control strategy can be defined to provide the necessary assurance of product quality.	Even though requirement on validation for “non-standard manufacturing process” is not new and was included also in the current guideline, requirement on non-standard manufacturing process validation was deleted from this section (and all other related sections as well). Wording was changed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Data are not required during the development phases, i.e. clinical phases I to III, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP ~~and non-standard manufacturing processes~~. ~~In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described~~.	
545	5.	Proposed change (if any): We suggest the addition of CFR (US Code of Federal Regulation) as an example in parenthesis (in addition to FCC).	Reference to CFR is not acceptable. Proposed change is not endorsed.
565-567	9.	Comment For some Investigational Medicinal Products (IMPs), e.g. radiolabelled IMPs where the proposed dose is a microdose (as per EMA/CPMP/ICH/286/1995) a justification can be provided for not conducting an assessment of related substances as part of a release and shelf-life specification. For drug substance in capsule or bottle IMPs release can be conducted on the basis of in-process controls of weight and appearance. Proposed change (if any): From	Radiolabelled IMPs are specific type of products. In lines 576 – 578 requirements on radiopharmaceuticals are defined. Related substances should be controlled in drug products in all phases of development (e.g. could be defined by ret. time in early development phases). Omission of this test is acceptable only in exceptional cases and should be always justified. Proposed change not supported

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. At least, tests on identity, assay and degradation products should be included for any pharmaceutical form. To The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. At least, tests on identity, assay and degradation products should be included for any pharmaceutical form unless otherwise justified.	
572-574	5.	Comment: Drug product tests should also take into consideration the stage of development and the practice of informing specifications and selecting appropriate acceptance criteria through development Proposed change: Drug product specific tests and acceptance criteria should be included in the specification in line with the pharmaceutical form used **and the stage of development** (e.g. dissolution **or disintegration in early development with an acceptable rationale, assay and uniformity of dosage units** for oral solid dosage forms, or pH, bacterial endotoxins and sterility for parenteral dosage forms).	It is stated in the scope of this guideline that the stage of development should be in general taken into consideration. Also below these requirements following sentence is included: The omission of drug product specific tests should be justified. Proposed change is not endorsed.
575	6.	Comment: Omission of test from the spec should be described in 2.2.1.P.5.6, if it is mentioned in 2.2.1.P.5.1.	Justification can be included in both sections 2.2.1.P.5.6 or 2.2.1.P.5.1 but it is not worthy to repeat the same

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		Proposed change (if any): Also add to 2.2.1.P.5.6.	requirements in different sections of the guideline. Therefore proposed change is not endorsed.
584 and 1103	5.	Comment: The recommendation is to align wording with DS section beginning at line 409-412. Specifically the following wording: It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General Considerations).	Proposed change is accepted. All relevant sections were updated.
600-602	8.	"*Batch results in a tabulated form or certificates of analysis for representative batches (same manufacturing site, same manufacturing process, same composition, and same batch size, unless otherwise justified,) to be used in the clinical trial should be provided.*" A representative batch is determined by a same manufacturing process, a same composition and a same batch size, whatever the manufacturing sites. Proposed change : "*Batch results in a tabulated form or certificates of analysis for representative batches (~~same manufacturing site,~~ same manufacturing process, same composition, and same batch size in the limit of 10 fold increase or downscaling down to 10-fold, unless otherwise justified,) to be used in the clinical trial should be provided.*"	This requirement is based on the Q&A document on the EMA web site. Requirement on data from each manufacturing site should be maintained. Proposed change is partly accepted. Requirement on "same batch size" was changed to "comparable batch size".
600- 609	5.	Comment: The examples cited for 'representative' are collectively very prescriptive and don't allow for a scientific	Current wording is in line with the Q&A requirements on the EMA web site.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		determination of what would be considered representative in relation to parameters with the potential to affect product quality and excludes the use of laboratory scale batches. The statement that the results should cover relevant strengths implies, but is not explicit, that a bracketed approach is acceptable; it would be beneficial to make this more explicit. Propose changes: Batch results in a tabulated form or certificates of analysis for representative batches (~~same manufacturing site,~~ ~~same~~ **similar** manufacturing process **and** ~~same~~ composition, ~~and same batch size~~, unless otherwise justified,) to be used in the clinical trial should be provided. The results should cover the relevant strengths to be used in the trial**, either utilising strength-specific data or a bracketing of strengths based on equivalent composition (e.g., capsules with different fill weights of same powder blend or granule)**. In case of **a complex manufacturing process conducted at** more than one ~~bulk~~ manufacturing sites, ~~it is necessary to provide~~ results **should be provided** for batches which have been produced by each of the ~~bulk~~ manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where **sites operate under a common quality system** ~~one legal entity has multiple sites (in the same country)~~, then batch analysis data from one site only would be sufficient).	Bracketting can be used for stability studies but not for batch analysis data. Proposed changes are not endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
600 - 611	1.	Comment: ACRO recommends adding guidance on the minimum number of batches on which analytical data should be provided to support each phase of clinical research. Proposed change (if any): Add guidance on the minimum number of batches on which analytical data should be provided to support each phase of clinical research.	Number of batches could differ for each type of drug product and it is not possible to recommend any specific number of batches. Proposed change not accepted.
606-609	6.	Comment: The requirement to provide data from each site, but then allowing an exception for a company that has multiple sites in the same country does not make sense. We request removal of the example. 'Unless otherwise justified' would support including a justification to support use of multiple sites where the process, scale, equipment is the same. Proposed change (if any) Re-word to say 'unless otherwise justified'.	This requirement is based on the Q&A document on EMA web site Proposed change is not accepted.
606 to 609	8.	"*In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which have been produced by each of the bulk manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch analysis data from one site only would be sufficient).*" Considering that a representative batch is determined by a same manufacturing process, a same composition and a same batch size (in the limit of 10- fold increase or	This requirement is based on the Q&A published on EMA web site Deletion of this paragraph is not supported.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		downscaling down to 10-fold) unless otherwise justified, this paragraph is not relevant. Proposed change: Deletion of this paragraph.	
630 to 632	1.	Comment: Frequently, for non-compendial packaging materials, sponsors are asked by some EU national regulatory authorities to confirm that the materials comply with applicable EU Directives and Regulations. This should therefore be noted in the guideline. Proposed change (if any): Include a statement that, where non-compendial materials are used, confirmation should be provided that the materials comply with applicable EU Directives and Regulations.	Sufficient information is provided in this section. Proposed change is not endorsed.
632-635	9.	Comment The need for extractables and leachables testing should take into consideration the constituents of the IMP and the Phase of development. Proposed change (if any): From For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), more details may be needed (e.g. extractable, leachable). For dosage forms where an interaction is unlikely, e.g. solid oral	The meaning of the sentence remains the same also after addition of the second part of the sentence. The possibility of justification for not providing any information on extractables or leachables is included in the original sentence as well. Proposed change is not supported but this requirement is now limited to phase III studies only.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		dosage forms, a justification for not providing any information may suffice. To For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenteral, ophthalmic products, oral solutions), more details may be needed taking into consideration the constituents of the IMP and the Phase of development (e.g. extractables, leachables). For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.	
634	5.	Comment: Data on extractables and leachables may not be available for early development (e.g. phase 1 or 2) , which should be fine if standard packaging components are used. Proposed change (if any): We recommend to limit the request to ~~phase 2 and~~ 3.	Proposed change is accepted. Requirement on extractables or leachables are limited to phase III studies only.
643	5.	Comment: As it is common to observe a trend during stability studies it is proposed to replace “No trend…” by “No unexpected trend and/or no trend resulting to a potential out of specification…”as a prerequisite for shelf life extrapolation Proposed change: “~~No~~ **Any observed** trends in stability	Rewording (in line with Q1E): No ~~trends~~ **significant changes** in stability behaviour are observed.

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		behaviour ~~are~~ observed **should be discussed to assure that the proposed shelf life extrapolation is justified"**	
646 - 648	1.	Comment: ACRO welcomes adoption of the concept that extrapolation of the shelf life for an investigational medicinal product may be based on an appropriately justified algorithm. The text states one example of "X + 12 months". However, X is not defined. Additionally, it would be helpful for Sponsors if the table provided on page 2 of the MHRA guidance document 'Points to consider when preparing the IMP dossier' is provided in this guideline. Three months real-time data 12 months shelf life Six months real-time data 18 months shelf life 12 months real-time data 24 months shelf life 24 months real-time data 36 months shelf life Proposed change (if any): Clarify the definition of X in the stated formula, and include the table provided on page 2 of the MHRA guidance document 'Points to consider when preparing the IMP dossier' in this guideline.	Proposed change accepted. The concept of extrapolation was revised to be more clear, X is defined as long-term stability data available. The MHRA guidance document was not implemented directly, but the same principles are applied.
646-648	5.	Comment: It is useful that this text allows some flexibility from the positions on extrapolation of stability data outlined in ICH Q1E. However, allowing only a four-fold extrapolation is not consistent with a science and risk based approach to	Drug products in clinical trial does not contain well-known drug substances, sometimes new forms are introduced and therefore their behaviour cannot be so easily predicted. It is not justified to have much more moderate conditions for shelf

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		stability studies. Alternative approaches to evaluating drug substance and drug product stability (e.g. using an accelerated stability assessment program to model the degradation according to the modified Arrhenius law – also referred to as ASAP modelling) can allow for extrapolation beyond an arbitrary 4x fold extension and beyond an extrapolation of X+12 months. It is helpful that the text concludes "other schemes may be possible and should be justified" but it might be preferable overall to provide NO arbitrary upper limits on allowed extrapolation without further justification (as even four-fold should be justified). Proposed change: The shelf life assigned should be based on the understanding of the stability of the product provided by the applicant. Depending on the data available, an extrapolation of real time data may be acceptable but should be justified (e.g. use of statistical plots, modelling and prediction tools, etc)	life extrapolation for clinical trial materials than for authorised products. It is important for Sponsors as well as Assessors to have some guidance. It is not possible to leave this only on responsibility of the Sponsor/Manufacturer. Proposed change is not endorsed, but the extrapolation requirements were reworded/clarified.
653	5.	Comment: The requirements for bulk drug product stability data and shelf life expectations is (1) an escalation of requirements and secondary to the specification in terms of assuring safety of the Drug Substance / Drug Product and (2) handled under GMP. Proposed change: ~~In case the drug product is stored in bulk for a significant time period, relevant stability data should be provided as~~	Storage in bulk (in different, mostly less protective, packaging material) can affect the stability of the drug product. Therefore, stability data to support storage in bulk are required. In case drug product is not stored in a bulk, no further data are needed and this does not lead to any escalation of requirements. Proposed change is not accepted.

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		~~well as shelf life, storage conditions and packaging material for the bulk.~~	
653 - 654	3.	Comment: What is the significant time period? Can it be clarified in this guideline?	For each type of product significant time period can be different (based also on the stability of the drug product/drug substance and bulk storage conditions), therefore it is not endorsed to write specific length of the storage.
653-654	7.	Comment: An indication of what is understood by *"a significant time period"* should be given. Proposed change (if any):	For each type of product significant time period can be different (based also on the stability of the drug product/drug substance and bulk storage conditions), therefore it is not endorsed to write specific length of the storage.
661 - 666	3.	Comment: In-use stability data might not be available at the time of CTA submission, especially in early development stage. In such case, the in-use stability data could be obtained prior to clinical study. We propose rewording this paragraph as following (i.e., to add underlined texts). Proposed change: *For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented, if available. In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay,*	In-use stability data are essential also for early development phases. In-use stability studies do not last so long, therefore it is not expected that this will cause big problems to Sponsors/Manufacturers. Proposed change was not accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		impurities, visible and sub-visible particles, microbial contamination/sterility). Shelf life and storage conditions after first opening and/or after reconstitution and/or dilution should be defined. <u>If the in-use stability data is not available, the in-use stability protocol, specifications and a statement that the data will be collected prior to the administration to patients, and in case specifications are not met the Sponsor will inform the CA should be provided.</u>	
663-666	8.	"*Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and sub-visible particles, microbial contamination/sterility).*" The sterility test performed by the applicant is not relevant and predictive after first opening, reconstitution or dilution by the investigator. Indeed, the sterility depends directly on the conditions under which the product is opened, diluted, reconstituted and stored by the user. Proposed change: "*In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and sub-visible particles, microbial contamination~~/sterility~~).*"	The requirement on sterility testing during in-use stability was deleted. Proposed change is accepted.
672 – 678 and 1026 - 1035	1.	Comment: ACRO welcomes the recognition that stability data on the investigational medicinal product may not be available at the start of a phase I clinical trial or a bioequivalence study, and agrees that these trials can be	IMP guideline does not cover all the possibilities of the study design. There are many new types (e.g. integrated protocol) In this case there is no problem to give condition that before the start of the phase II study stability results should be

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		supported by relevant data from development studies, with a stability programme using a relevant batch or batches of the product initiated prior to the start of the clinical trial. However, clinical trial protocols for investigational medicinal products early in clinical development often combine both phase I and phase II aspects, therefore ACRO recommends that the guideline should specify the requirements for this situation. Proposed change (if any): Specify the stability testing requirements to support clinical trial protocols that combine phase I and II aspects of clinical development.	provided. The same situation is in the clinical part, often submission of phase I data before start of the phase II study is required. Proposed change is not acceptable.
691 - 695	1.	Comment: This section includes as 'authorized' products also those from ICH-regions and Mutual Recognition Agreement (MRA)-partner countries. However, the definitions of 'authorized' products in article 2, sections (9) and (10) of regulation 536/2014, do not include ICH-countries or MRA-partner countries. Furthermore, section 52, table 1 of Annex I of Regulation 536/2014 distinguishes between 'authorized' IMP [i.e. those within the scope of definitions given in article 2, sections (9) and (10)] and products that have a 'marketing authorization in an ICH country', while 'MRA-partner countries' are not mentioned. Clarification should be sought, how the inclusion of MRA-partner countries in this section of the guidance is covered by the regulation 536/2014. Proposed change (if any): To adapt the wording to read "For	Reference to (MRA)-partner countries and acceptance of marketing authorisations from MRA partner countries was deleted from the whole guideline, because it is not in line with the Regulation No. 536/2014 and up to now EC has not published any statement to this topic. No other rewording of this section is needed. Proposed change partly accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		test and comparator products to be used in clinical trials which have already been authorised in the EU/EEA, or have a marketing authorization in one of the ICH-regions it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA, incl. copy of the SmPC/Summary of Product Characteristics or its equivalent e.g. Prescribing information."	
691-701	5.	Comment: According to Line 691-695, for products authorised in EU/EEA, ICH-regions or MRA-partner countries can be submitted with limited information (name of MA-Holder, MA number, and SmPC). According to line 669-701, if the products are sourced from outside EU/EEA, MRA-partner countries or ICH regions, a full IMPD should be submitted (Line 699). Does this imply that if the product is authorised in EU/EEA, MRA-partner countries, or ICH regions, but sourced from outside these countries, a full IMPD needs to be provided? Please elaborate. Proposed change (if any): Please elaborate.	The requirement is quite clear. Drug products authorised in EU/EEA or ICH are accepted for clinical trials with SmPC or equivalent, no full IMPD has to be submitted. Drug products authorised in "third countries" can also be used in clinical trials but full IMPD has to be provided because are considered as non-authorised from our point of view. In case reference to product authorised e.g. in Germany is made, this product can be sourced directly from Germany or product intended for German market sourced directly from manufacturer can be used. In case the drug product was sourced directly from Manufacturer, but was not intended for German market, but e.g. for South Korea, submission of statement that the product is the same as for German market is not sufficient and full IMPD should be provided. Following wording was added for clarification: …**(and are sourced from these countries),** it will be sufficient… Reference to MRA-partner countries was deleted because this

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			is not in line with the Regulation no. 536/2014.
693-694	5.	Comment: The sentence should be more precise as to the location of the relevant information. Proposed change (if any): …will be sufficient to provide the name of the MA-holder and the MA-number **in the clinical trial application form** as proof for the existence of a MA, incl. copy of the SmPC/Summary of Product Characteristics or its equivalent e.g. Prescribing information **in Module 1**.	This guideline covers requirements on information which should be included in the IMPD, not in the Clinical Trial Application form. Information in the IMPD and Application form should have been consistent, but new Application form will be used and it is not clear which information will be included. Proposed change not accepted.
697 - 698	5.	Comment: To prevent the unnecessary submission of amendments; the expiry date of authorised non-modified should not be included in the quality section of the dossier Proposed Change: For authorised, not modified products, it will be sufficient to state the respective expiry date assigned by the manufacturer **on the label**.	This requirement was slightly modified, now statement that respective expiry date assigned by the manufacturer will be used, is sufficient. Therefore in case expiry date of authorised product is changed, no modification has to be submitted. Proposed change not accepted.
702 - 825	1.	Comment: The guidance should specify what 'modification' entails, and when an IMPD/auxiliary medicinal product dossier should be prepared in accordance with this guidance following sections 52 and 55 of Annex I of Regulation 536/2014. It should preferably give guidance on which of the following are included as falling under 'modification': • Trial-specific operations that could affect the product	It is not possible to create and exhaustive lists of modifications of authorised products. Every difference to the approved dossier for marketing authorisation is taken as modification (e.g. different packaging sites, different container)… Proposed change is not endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		quality, such as o Modification of the pharmaceutical form (e.g. over-encapsulation, trial specific colour or coating, dilution, re-tableting for blinding etc.) or o Primary re-packing (e.g. removal from the immediate container and repacking into another immediate packing. • Secondary packaging, i.e. any other placing the medicinal product, which is already sealed within its primary packaging material into a trial-specific different outer packaging material • Trial-specific assembly Trial-specific labelling with no other primary or secondary packaging (Article 2, sections (9) and (10) of regulation 536/2014 exclude 'changes to the labelling'. This is of relevance, where a comparator has a marketing authorization (MA) in multiple EU Member States, and the sponsor chooses to use the IMP registered in Germany for the purposes of the trial, it will be sufficient to provide the name of the German MA-holder and MA-number as proof for the existence of a MA, incl. copy of its Summary of Product Characteristics. However, as the marketing authorisation holder (MAH) of the comparator product is only responsible for the unchanged product in its designated and authorised (German) packaging, it should be specified if the sole	

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		addition of a clinical trial specific labelling will constitute a modification of the comparator or not. Proposed change (if any): Provide more detailed guidance on what comprises modification of an authorised comparator/auxiliary medicinal product.	
704 - 705	1.	Comment: 'Study' (i.e. clinical study) or 'clinical trial' should be consistently used in this guidance in line with the definitions given in article 2 of regulation 536/2014, and the use of modified comparator products is not necessarily limited to blinded studies. Proposed change (if any): Change wording to "In preparing supplies for clinical trials, applicants often modify or process medicinal products which have already been authorised in order to use them as comparator products in clinical trials blinded studies."	Term "Clinical trial" is used in the guideline which is in line with the Regulation (EU) no 536/2014. The whole document has been revised accordingly. In the sentence there is written "often" which does not mean that modified products are used only in blinded studies. The sentence is only introduction, it is proposed not to modify this sentence. Proposed change not endorsed. But information on test products was added to this section, because authorised modified products can be used as test products as well.
712-713	6.	Comment: It is interpreted as the quantitative composition of the comparator product should be included. This is proprietary information and cannot be provided. Please add 'unless justified otherwise'. Proposed change (if any) Add 'unless justified otherwise'	This is no new requirement, this used to be in the currently valid guideline. In case drug product is modified other than by repackaging, it is highly probably that the composition was modified (e.g. different coating material, encapsulation) and then quantitative composition should be provided. Proposed change is not endorsed.

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738 – 742	1.	Comment: Wording should match with corresponding other sections in the guidance (lines 512 – 516, 934 – 937, 1055 – 1059) and of article 61, section 5 (a) of regulation 536/2014 and include re-packaging and or re-labelling. Proposed change (if any): To include 'labelling', e.g. "When packaging *and or labelling* is carried out at a hospital, health centre or clinic where the investigational medicinal 738 product is to be used for the trial exclusively at that institution, […]"	Proposed change accepted. Labelling was added to the sentence. Packaging and labelling were changed to re-packaging and re-labelling to be in line with Regulation (EU) 536/2014.
754	1.	Comment: There is a typo (additional Space after "film-"): "film- coating" Proposed change (if any): "film-coating"	Change accepted.
787-790	6.	Comment: The requirement to provide data from each site, but then allowing an exception for a company that has multiple sites in the same country doesn't make any sense. We request removal of the example. 'Unless otherwise justified' would support including a justification to support use of multiple sites where the process, scale, equipment is the same. Proposed change (if any) Re-word to say 'unless otherwise justified'.	This requirement is based on the Q&A document on EMA web site Proposed change not accepted.
787-790	8.	"*In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which have been*	This requirement is based on the Q&A published on EMA web site

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		produced by each of the bulk manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch analysis data from one site only would be sufficient)." In accordance with the comment on lines 606-609, we propose to delete this paragraph.	Deletion of this paragraph is not supported.
810	1.	Comment: Frequently, for non-compendial packaging materials, sponsors are asked by some EU national regulatory authorities to confirm that the materials comply with applicable EUC Directives and Regulations. This should therefore be noted in the guideline. Proposed change (if any): Include a statement that, where non-compendial materials are used, confirmation should be provided that the materials comply with applicable EU Directives and Regulations.	Sufficient information is provided in this section, only one sentence was added to be in line with the requirements in section 2.2.1.P.7 Proposed change is not endorsed.
Line 822	3.	Comment: We propose adding the following texts after Line 822, in accordance with section 2.2.1.P.8 Stability (add underlined texts). Proposed change: *Any proposal for a future shelf life extension without substantial modification submission should be stated in the IMPD. Stability protocol, shelf life extension plan and a*	Information in this section should be consistent with the same section for investigational medicinal products. Shelf life extension without substantial modification submission could be acceptable under the same conditions as are valid for IMPs (section 2.2.1.P.8) Proposed wording not accepted, but the section was updated with new information.

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		statement that in case of any significant negative trend the Sponsor will inform the competent authority should be provided. The stability protocol should cover the maximum planned shelf life.	
823	5.	Comment: Clarify that in-use stability studies are only required where modifications may have an impact on “in-use" stability: In-use stability studies should be performed where modifications may have an impact on “in-use" stability in the case of use of the comparator product in different conditions ~~as~~ to those described in the SPC (according to the clinical protocol), if not otherwise justified.	No further clarification is needed. It is possible to justify missing in-use stability data, e.g. using a statement that modifications have no impact on the stability. Proposed change is not endorsed.
Line 824	3.	Comment: We propose adding the following texts after Line 824, in accordance with section 2.2.1.P.8 Stability and also with our proposal to Line 822 as mentioned above (add underlined texts). Proposed change (if any): *For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented, if available. In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay,*	Proposed change was accepted, reference to requirements defined in section 2.2.1.P.8 is now included.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		impurities, visible and sub-visible particles, microbial contamination/sterility). Shelf life and storage conditions after first opening and/or after reconstitution and/or dilution should be defined. If the in-use stability data is not available, the in-use stability protocol, specifications and a statement that the data will be collected prior to the administration to patients, and in case specifications are not met the Sponsor will inform the CA should be provided.	
872 - 873	5.	Comment: With regard to the text - "Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification), if relevant.", for a product that complies with a compendial monograph unless information on potential genotoxic impurities are included in the monograph it is not clear to industry how to address this requirement when information on the manufacturing process will not be available. The proposal would be therefore to remove this section of text Proposed change (if any): "~~Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification), if relevant.~~"	Not all drug substances which are used for BE studies are compendial. For substances that comply with a compendial monograph, sufficient information on the manufacturing process of the active substance should be provided (see section 1.5) Proposed change is not endorsed.
829 - 831	1.	Comment: This section of the guideline refers back to previous sections with regard to the required information on the active substance and finished product of a reference	It is hard to specify age of the samples of reference products. No guidance can be given in this point, this is fully in responsibility of the Sponsor.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		comparator/innovator product used during the development of a generic product. However, when a comparison study with the originator product is performed to analyse various parameters as part of the pharmaceutical development of a generic product, ACRO recommends that it would be helpful to include guidance on selecting the age of the samples of reference product to be considered equivalent to the generic (as marketed reference product will be exposed to different conditions from generic products under development). This is especially important for sensitive products like dry powder inhalers and will help in generating uniform data throughout the Generics industry. Proposed change (if any): Add guidance on selecting the age of the samples of reference comparator/innovator product to be considered equivalent to the generic product when a comparison study with the reference product is performed to analyse various parameters as part of the pharmaceutical development of a generic product.	Proposed change is not accepted.
920	1.	Comment: More guidance should be provided here as some regulatory authorities routinely ask for sponsors to confirm that the components of the drug substance container closure system comply with applicable Ph.Eur monographs, EC Directives and EC Regulations. Proposed change (if any): Describe in more detail the information that is required on the drug substance	Sufficient information is provided in this section, only one sentence was added to be in line with the requirements in section 2.2.1.S.6

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		packaging system.	
928	1.	Comment: More guidance should be provided here regarding the pharmaceutical form for the drug product. Sponsors should be encouraged to use one of the standard terms in the EDQM Standard Terms database. For example, some sponsors often use the term 'solution for injection' in the IMPD to describe the IMP, which does not match the route of administration described in the clinical trial protocol where the IMP will be administered by intravenous infusion. Proposed change (if any): Encourage use of standard terminology from the EDQM Standard Terms database.	Proposal accepted. Addition of sentence: Standard terminology from the EDQM Standard Terms database should be preferably used for dosage forms, where applicable.
951-954	1.	Comment: While ACRO concurs that, in general, information on process validation and/or evaluation is not applicable for a risk assessment of finished products intended for clinical trial use, in the case of sterile products manufactured using aseptic processes, ACRO suggests including the recommendations provided in the guideline for biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs, in order to demonstrate the efficacy of aseptic processing operations. Proposed change (if any): In the case of sterile products manufactured using aseptic processes, include the recommendations provided in the guideline for	In most cases bioequivalence studies are performed with solid oral dosage forms, therefore in this section stated information is sufficient, no further details are needed. Proposed change is not endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs.	
1021-1022	1.	Comment: Frequently, for non-compendial packaging materials, sponsors are asked by some EU national regulatory authorities to confirm that the materials comply with applicable EUC Directives and Regulations. This should therefore be noted in the guideline. Proposed change (if any): Include a statement that, where non-compendial materials are used, confirmation should be provided that the materials comply with applicable EU Directives and Regulations	Sufficient information is provided in this section. Proposed change is not endorsed.
1034-1035	8.	"*Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study*" Shelf-life extrapolation is not defined in this paragraph and should be added as it is done in the paragraph 2.2.1.P.8. to the guideline (See lines 640 to 660). Proposed change: "*Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study. Shelf-life extrapolation may be made according to conditions described in section 2.2.1.P.8.*"	Requirements on stability data and extrapolation are for bioequivalence studies not so strict, because known drug substances and drug products with the same or similar composition as originator product are used. No change has been made to this section in comparison to the currently valid guideline. Proposed change is not supported.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
1068	1.	Comment: While ACRO concurs that, in general, information on process validation and/or evaluation is not applicable for a risk assessment of finished products intended for clinical trial use, in the case of sterile products manufactured using aseptic processes, ACRO suggests including the recommendations provided in the guideline for biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs, in order to demonstrate the efficacy of aseptic processing operations. Proposed change (if any): In the case of sterile products manufactured using aseptic processes, include the recommendations provided in the guideline for biopharmaceuticals (EMA/CHMP/BWP/534898/2008) for information connected directly to the safety of the product (such as bioburden prior to filtration) and information about media fill runs.	Proposed change is acceptable, reference to requirements in section 2.2.1.P.3.4 was made.
1105-1106	1.	Comment: Frequently, for non-compendial packaging materials, sponsors are asked by some EU national regulatory authorities to confirm that the materials comply with applicable EUC Directives and Regulations. This should therefore be noted in the guideline. Proposed change (if any): Include a statement that, where non-compendial materials are used, confirmation should be provided that the materials comply with applicable EU	Sufficient information is provided in this section. Proposed change is not endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Directives and RegulationsComment	
1135	5.	Comment: - 2.1.A.3 : should excipient from recombinant origin never formulated in a registered product, be documented in this section when the corresponding excipient derived from animal or human origin is already used in the formulation of a registered product?	In case known excipient is newly of recombinant origin, instead of animal or human origin, relevant documentation, which complies to CHMP/BWP/534898/2008 rev.1, should be provided.
1138- 1140	5.	Comment: It would be helpful to provide some guidance on where in the quality documentation information on the solvents for reconstitution and diluents should be located. Alignment with the guidance included in ICH M4/M8 would be helpful and provide consistency. Proposed change: **'For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P", as appropriate'**	There is no reason to more specify where the information on diluents should be situated in the IMPD, it is important that relevant data are provided. Some Sponsors follow the guideline and information on solvents and diluents can be found in appendices, some Sponsors include information on the diluents in a separate part "P". Both possibilities are acceptable. Proposed change is not accepted.
1141 - 1144	1.	Comment: According to the proposed guidance, the marketing authorisation holder (MAH) of the comparator product is only responsible for the unchanged product in its designated and authorised (e.g., German) packaging. Where an auxiliary medicinal product has a marketing authorization (MA) in multiple EU Member States, and the sponsor chooses to use the IMP registered in, for example, Germany for the purposes of the trial, the guidance should specify if the sole addition of a clinical trial specific labelling into national language(s) of other Member States will constitute	Requirements on auxilliary medicinal products are now according to the Regulation the same as for investigational medicinal products Labelling on all products should be in national language. This is more thing of Regulation interpretation. Proposed change is not endorsed.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		a modification in accordance with Article 65 of regulation 536/2014 or not. The guidance should further clarify here whether no auxiliary medicinal product dossier (SmPC or simplified dossier as applicable) will be required for such authorized auxiliary medicinal product, in accordance with section 55, table 1 of Annex I of Regulation 536/2014. Proposed change (if any): Describe in more detail whether the sole addition of a clinical trial specific labelling into national language(s) of other Member States will constitute a modification in accordance with Article 65 of regulation 536/2014 or not, and any need for an auxiliary medicinal product dossier under such circumstances.	
1145 - 1152	1.	Comment: This section refers to changes to investigational medicinal product. It should also indicate that such changes shall also be considered for auxiliary medicinal products as applicable. Proposed change (if any): Include auxiliary medicinal products in section header “Changes to the investigational medicinal product or auxiliary medicinal product with a need to request a substantial modification to the IMPD/auxiliary medicinal product dossier”, and add a sentence in the guidance text to include auxiliary medicinal products for changes and request for substantial modification, e.g. “The guidance in this section should also be referred to for	Proposed change accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		auxiliary medicinal products as applicable."	
1145-1176	5.	Comment: It was acknowledged that this table was amended. With regard to the examples of changes, we would appreciate having more included to have EU harmonized view on those as well. See below proposals for addition, together with our assessment. Proposed change (if any): S4: Under changes to 'specifications of drug substance' add 'Tightening of specifications (no safety concern' which is considered a non-substantial change *(similar approach as for changes to specifications of the medicinal product)* S4, P5: Under changes to 'specifications of drug substance' and 'specifications of the medicinal product' add 'Addition of tests (no safety reason)' which is considered a non-substantial change S7: Add for the drug substance *(similar to the medicinal product)* that 1) an extension of retest period (based on additional stability data in accordance with approved extension scheme with unchanged specifications) which is considered a non-substantial change, and 2) a reduction of retest period which is considered a substantial change. P1, P5: Add for the medicinal product clarification that changes in tablet imprint are regarded as non-substantial change (no impact on functionality)	The list cannot be exhaustive there are many possibilities, only some changes were accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		P3: Formal Name changes in manufacturer(s) are considered non-substantial.	
1146 Headings in table 1 2 and 3	5.	Comment: Suggest retain the term 'amendment' rather than change to 'modification' Proposed Change: …need to request a substantial **amendment** ~~modification~~ to the IMPD	Term modification is in line with Regulation. Proposed change is not supported.
1152 – 1178 and Tables 1, 2 and 3	1.	Comment: The list of examples and examples given in tables 1 and 2 should match. "Manufacturer(s) of the medicinal product" is included in table 2 but not listed in the body text of this section. Proposed change (if any): Add "Manufacturer(s) of the medicinal product." to the body text of this section.	Proposed change accepted.
1155	1.	Comment: In order to provide clarity it would be helpful for sponsors if more information is provided here. For example, for a product which is diluted prior to intravenous administration, does immediate packaging material just refer to the drug product container closure system (glass vial and stopper) or does it also refer to the material from which the infusion bag is manufactured? Additionally, it should be noted that n-use stability data needs to be provided in the IMPD which covers the practice described in the clinical trial protocol. Proposed change (if any): Expand the guidance to explain more about the requirements for changes to the immediate	Term immediate packaging material was changed to container closure system and Table 1 was updated accordingly. More detailed guidance which changes in container closure system are considered substantial is now included in the Table 1.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		packaging material that will represent a substantial modification to the IMPD.	
1177-1178	5.	Comment: Text format is recommended for clarity Proposed change (if any): Test procedures of non-pharmacopoeial excipients are only to be regarded as “substantial” where they are likely to have a significant impact on: …	Typo error, it is wrong only in the document published on the EMA web site Proposed change not accepted.
1179 - 1182	1.	Comment: The classification criteria for “substantial” listed in this section are based on wording following current Directive 2001/20/EC and detailed guidance CT-1: – The safety or physical or mental integrity of the patients; – The scientific values of the trial; – The conduct or management of the trial; – The quality or safety of any IMP used in the trial. Criteria should be aligned with the definition following article 2, section (13) of regulation 536/2014, where “The conduct or management of the trial” or “the quality or safety of any IMP used in the trial” are not explicitly stated. Proposed change (if any): Change wording to align with definition of article 2, section (13) regulation 536/2014, stating:	There was typo error in the published document. More detailed information is provided in the document.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		"[…] are only to be regarded as "substantial" where they are likely to have a significant impact on: – The safety or rights of the subjects, or on – The reliability of the robustness of the data generated in the clinical trial" If further details to this definition are needed for changes to medicinal product quality, and if permitted by the definition given in the Regulation 536/2014, the additional points should be added for supportive clarification, e.g. "'Substantial' shall also entail a change with significant impact on the quality or safety, or management of any IMP or auxiliary medicinal product used in the trial".	
1182 and tables	5.	Comment: The previous guideline included text on substantial amendments which would be helpful to maintain in order to provide clarity to the cited examples, the tabular listings and to provide context for change control assessments by the sponsor. Proposed change: Retain previous text which served as good guidance and include table headings for clarity In all cases, an amendment is only to be regarded as "substantial" when one or more of the above criteria are met. The list is not exhaustive; a substantial amendment	There was a typo error which appeared during conversion to pdf format, required text is still included in the guideline but was inadvertently omitted in the published document.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		might occur in some other aspect of a clinical trial. Assessment of an IMPD should be focussed on patient safety. Therefore, any amendment involving a potential new risk has to be considered a substantial amendment. This may be especially the case for changes in impurities, microbial contamination, viral safety, TSE and in some particular cases to stability when toxic degradation products may be generated. The amendments refer to the submitted IMPD. Should the changes be covered by the IMPD as submitted, a notification of a substantial amendment will not be necessary. When an amendment will become effective with the start of a new clinical trial (e.g. change of name of the IMP, new manufacturing process), the notification will take place with the application for the new trial. Notifications of substantial amendments are only necessary for changes in ongoing clinical trials. The following tables cite examples for changes and whether notification of a substantial amendment is required. This list does not claim to be exhaustive. The sponsor should decide on a case by case basis if an amendment is to be classified as substantial or not.	
Table 2	5.	Comment: Line “manufacturing process of the drug substance”:	Proposed change is acceptable.

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		Proposed change (if any): Delete “same reagents” in the parenthesis in the box “Modifications of the process parameters” as e.g. a change from NaOH to KOH is minor and no notification should be needed.	
Table 2 manufacturer of the drug product	5.	Comment: The addition of any drug product manufacturing site is considered to be substantial. However, considering the impact on the impact on the safety of the patient/healthy volunteer additional analytical testing sites and packaging/labelling sites should be considered non-substantial, provided that appropriate GMP evidence is internally available. Proposed change: For “Manufacturer(s) of the medicinal product, add to the non-substantial column: Addition of drug product testing sites and packaging sites	For all sites relevant GMP documents should be provided, therefore this is considered as substantial modification. Proposed change is not endorsed.
Table 2		Comment: There should be scope for justifying changes as non-substantial. E.g. where testing function is added – if the site is already in the IMPD the change should be able to be justified as non-substantial. Proposed change (if any) :	Only most common examples are included in the table. The list is not exhaustive, not all changes can be included in the table. Proposed change not supported.
Table 2 and	1.	Comment: For clarity, ACRO recommends adding “addition of tests (no safety reason)” and “tightening of acceptance criteria (no safety reason)” to the “not required” column for both active substance and investigational medicinal product.	Addition of tests and tightening of acceptance criteria (no safety reason) was added to column “not required” for drug substance and drug product specifications.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Table 3		Additionally, ACRO recommends that the final guideline should include a more comprehensive and detailed list of examples of changes that will warrant a substantial modification. Current guidance on changes that will require a substantial amendment is incomplete and therefore remains open to differences of interpretation by both applicants and assessors. Proposed change (if any): Add “addition of tests (no safety reason)” and “tightening of acceptance criteria (no safety reason)” to the “not required” column for both active substance and investigational medicinal product, and include a more comprehensive and detailed list of examples of changes that will warrant a substantial modification.	Otherwise, the list cannot be exhaustive, because there could be many specific changes. Only the most common examples are stated in this section. Proposed change partly accepted.
Table 3 Shelf-life	1.	Comment: The guidance should include the possibility to file a shelf-life extension plan not only with the initial filing but also later as a substantial modification. Proposed change (if any): Include in both columns the possibility of a later substantial modification approval e.g. “[…] with the initial *or a previous substantial modification* filing of the IMPD […]”	Reference to previous substantial modification was added to table 3. Proposed change accepted.
Table 3	5.	We suggest that ‘CoA for new batch of the medicinal product’ is deleted since data from a new batch should not be seen as an amendment to what has previously been submitted.	There are still many Sponsors that provide CoA for every new batch which will be used in the clinical trial in form of amendments, therefore this line has been added to clearly state that this is not a substantial modification and there is no

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		In the event that data from a new batch leads to a need to amend any existing details, then this would be covered by one of the other examples. Proposed change: Delete row about 'CoA for new batch of the medicinal product'	need to be provided separately. Proposed change not endorsed.