14 September 2017
EMA/CHMP/BWP/563769/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials' (EMA/CHMP/BWP/534898/2008 rev. 1)

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	Advanced Accelerator Applications
3	CSL Limited and CSL Behring
4	European Biopharmaceutical Enterprises (EBE)
5	EuropaBio
6	Dawn Spark, Kyowa Kirin Limited
7	Biosimilar Medicines Group, a sector group of Medicines for Europe
8	Pierre Fabre Médicament
9	Vaccines Europe (VE)
10	Transgene S.A.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome
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 for quality documentation concerning biological investigational medicinal products in clinical trial. However, ACRO believes that it could be strengthened by closer alignment with the equivalent guidance (currently in revised draft form) on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015). In particular, ACRO recommends that greater emphasis is given to the following principles: • Adoption of a risk-based approach to documentation requirements focused on risk aspects of the investigational medicinal	The comment is noted The wording in the guideline is such that these principles are included

Stakeholder no.	General comment (if any)	Outcome
	product, taking into account not only the nature of the product and the state of development/clinical phase, but also the patient population, nature and severity of the indication and the characteristics of the proposed clinical trial. • An 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.	
	A related companion document is the template for the Qualified Person's (QP) Declaration of Equivalence to EU GMP for Investigational Medicinal Products Manufactured in Third Countries (ARTICLE 13(3)(b) OF DIRECTIVE 2001/20/EC). http://ec.europa.eu/health/files/eudralex/vol-10/2013-12_qp_template_imp.pdf	The QP declaration is not subject of the guideline
	ACRO recommends that the QP Declaration template cross-reference the revised Quality Guideline and that links between the IMPD and the QP Declaration should be clarified in the Guideline, especially with respect to • the listing of manufacturing sites (substance and/or product) and • GMP Certification evidence harmonisation across competent authorities (i.e., for biological / biotechnological drug substances without an MA in the EU and manufactured in a third country). Additionally, ACRO recommends that it should be made clear that the guideline does not address any requirements associated with	This is not within the scope of the guideline

Stakeholder no.	General comment (if any)	Outcome
	manufacturing and/or import authorisations which will, presumably, be addressed in separate legislation and/or guidelines.	
3	This Sponsor supports the proposed grouping of Phase I and II clinical trials together in relation to the sections on specifications and validation of analytical procedures, as opposed to the current guideline in which Phase II and III are grouped together (e.g. line numbers 273, 288, 294, 518).	No comment required
4	EBE very much welcomes the opportunity to provide comments on this important EMA-BWP Guideline revision. It is noted that previously, requirements for Ph II were at the same level as for Ph III. In the revised guidance Ph II requirements are at the level of Ph I. We appreciate this change since this reduces the burden for the Ph II trials at a time of development when product-specific knowledge is still very limited. It would be helpful if in a future revision to this guidance quality for radio labelled biological products used in human clinical studies was included, where the intended biological for development is a non-radio labelled biological product. The aim of this guideline is to define harmonised requirements for the documentation to be submitted throughout the European Union. Whilst appreciating that the requirements defined in this guideline can only be taken as illustrative rather than an exhaustive list, there is concern that despite this revision, the detailed requirements for quality and GMP information for an IMP may not be uniformly understood across the member state agencies in connection with Regulation (EU) No.536/2014. Currently, using the national	The comment is noted

Stakeholder no.	General comment (if any)	Outcome
	submissions procedure, different levels of quality information are required across member states. A harmonised risk based approach should be applied to the assessment of the quality information. The level of detail should ensure patient safety and still provide the Sponsor sufficient flexibility to develop and optimise manufacture of a high quality product. Risk-based approaches are seen as a mechanism to achieve the required balance of registered information to protect patients. Additional guidance or examples through Q&As may prove beneficial.	The comment is noted
5	EuropaBio welcomes the opportunity to respond to this consultation on the draft Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008 rev. 1). This guideline which defines the requirements for quality documentation submitted in support of clinical trial applications is of particular interest to our members involved in clinical development of biological / biotechnology derived medicinal products. We have consulted with our members and provided EuropaBio's comments and observations on the revised guideline. We hope that they are helpful in improving the guideline with greater clarity.	The comment is noted
7	The Biosimilar Medicines Group welcomes and appreciates the unique opportunity to share our opinion and comments on the draft guideline. The list of detailed comments is available on the next pages.	The comment is noted

Stakeholder no.	General comment (if any)	Outcome
9	General request for clarification on whether the principles of this guidance also apply to vaccines. The recommendation is to keep the guidance as flexible as possible for alternative vaccine approaches for which other characterization techniques are used as described in the guidance. It would be of benefit to have specific vaccine quality guidance that cross-references this biological guidance where appropriate.	The comment is noted

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
53	4	**Comment:** It is important to make phase-dependent distinction for phase I and phase II compared to phase III to accommodate the very limited manufacturing experience and batch data for a given product at phase I/II. At early phase the Sponsor should be able to employ risk-based approaches that include use of prior experience and knowledge, for a similar class of product manufactured by the Sponsor and use of published literature, in addition to the focus on patient safety. The specifications and process controls for such phase I/II studies should be wide enough to allow manufacture and release of the product until phase III and re-evaluation of the specifications and control limits. It would be helpful for the Objective section to reinforce phase-dependent expectations throughout the IMPD and use of greater risk-based approaches at phase I/II while assuring patient safety. **Proposed change:** Additional paragraph on risk-based approaches and 'prior knowledge'; The control strategy in early development should be focussed on patient safety. In phase I/II, when manufacturing experience of the product is limited, the Sponsor may justify use of risk-based approaches that may include use of prior experience and knowledge, for a similar	Not accepted. The guideline provides sufficient flexibility to allow use of prior knowledge where relevant and justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		class of product manufactured by the Sponsor and use of published literature. At phase III, the specifications and control limits would be re-evaluated.	
93-94	4	**Comment:** Only medication **not** being part of the patients' usual medicines should be regarded as auxiliary medicinal products and delivered by the sponsor. Examples of these are rescue medication and therapy new to the patient and required by the inclusion criteria. Background medication already used by the patient and prescribed by their physician, should **not** be supplied by the sponsor as part of the clinical trial. Consequently, as the products will be used according to a valid marketing authorisation (and obtained by the patient directly from the pharmacy), there should be no requirements to include Q-IMPD documentation for these products in the clinical trial application. The ethical aspect should also be considered, as supplying these products could influence the patients' willingness to participate in the trial. It would be helpful to align wording on AMPs with draft guidance EMA/CHMP/QWP 834816/2015 and refer to the AMP/IMP definitions document that is under revision.	Partly accepted. A sentence to provide more clarity is included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ~~'The guideline also applies to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances.~~' **Replace with…** "For auxiliary medicinal products (AMP), supplied by the Sponsor as part of the clinical trial, the same requirements and principles apply as for investigational medicinal products. The requirements depend on the type of the product (authorised / not authorised /modified / non-modified medicinal product). For definitions of AMP versus IMP, refer to "Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)" in preparation for the implementation for the Clinical Trials Regulation (EU) No 536/2014".	
93-94	5	**Comment:** Only medication **not** being part of the patients' usual medicines should be regarded as auxiliary medicinal products and provided by the sponsor. Background medication already used by the patient and prescribed by their physician, should **no**t be supplied by the sponsor as part of the clinical trial. Consequently, as the products will be used according to a valid marketing authorisation (and bought by the patient directly from the pharmacy), there should be no requirements to include Q-IMPD documentation for these products in the clinical trial application.	Partly accepted. A sentence to provide more clarity has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		There are also ethical considerations, as supplying these products could influence the patients' willingness to participate in the trial. **Proposed change:** We would suggest revising as follows: The guideline also applies to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances **where documentation on the Auxiliary Medicinal Product is required to be submitted by the Sponsor in accordance with Regulation (EU) No 536/2014.**	
96 - 97	4	**Comment:** While devices are quoted in diverse sections of the guidance (P.1/P.7), the device piece is not mentioned in the scope of the guidance. IMP/Devices should be part of this guideline as long as the primary mode of action is led by the IMP and not the device. Radio-labelled antibodies are not included in this guidance although inclusion would have been useful (see General Comment). **Proposed change:** "IMP/Devices are part of this guideline when the primary mode of action is led by the IMP and not the device. Radio-labeled antibodies are excluded from the scope	Not accepted. The scope of the guideline are IMPs containing proteins /peptides, independent of the use of devices Radio-labelled antibodies are not per se excluded from the guideline. However, the conjugate is not specifically addressed in this guideline. Please refer to the "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" (CHMP/QWP/185401/2004).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of this guideline."	
99	3	**Comment:** Reference to detailed guidelines implies that phase appropriate GMP is no longer accepted – propose to remove. **Proposed change:** IMPs should be produced in accordance with the principles and the detailed guidelines of good manufacturing practices for medicinal products (The rules governing medicinal products in the European Community, Volume IV).	Not accepted. IMPs need to be manufactured in accordance with EU GMP.
103 - 105	1	**Comment:** Confusion still exists as to whether the IMPD should contain the Non-clinical and Clinical information on the IMP, when the Investigator Brochure already covers this. In order to avoid having similar information contained in two documents (which are not always updated at the same time and may be reviewed by different assessors), ACRO recommends that the proposed guideline should specify the Non-Clinical and Clinical information should remain the remit of the Investigator Brochure, with the IMPD solely containing the Quality information. **Proposed change:** Add a statement to confirm that the Non-Clinical and Clinical information should remain the remit of the Investigator Brochure, with the IMPD solely containing the Quality information.	Not accepted. The requested addition is not within the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
105	4	**Comment:** Duplicated information in the IMPD results in more complex updates. Information should be given only once and then referenced. **Proposed change:** In Section 1.4. suggest to insert: "**Duplication of information should be avoided as much as possible throughout the application. Appropriate use of cross-referencing should be employed**."	Not accepted. The current structure should be maintained as it is not considered to contain too much duplication of information.
106 - 112	4	**Comment:** The whole paragraph could lead to confusion as it is difficult to understand if it only refers to an approved drug substance or also covers the approved finished drug product. In the guidance EMA/CHMP/QWP/834816/2015 "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" the same wording is provided under 5.2.1.S Drug substance. 'A statement should be provided that the active substance has the same quality as in the approved product.' Suggest this requirement for a 'statement' is removed, it should be sufficient to follow the requirements of the simplified IMPD cited in Table 1 of regulation 536/2014 (line 112). **Proposed change:** "If the Active substance used is already authorized in a ~~finished~~ **drug** product within the EU/EEA, in one of the ICH regions or one of the	Not accepted. Active substances cannot be approved, only medicinal products. If reference is made to an authorised product the active substance should have the same quality as in an approved product, otherwise reference cannot be made. Use of the term "finished product" rather than "drug product" is in line with EU terminology.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Mutual Recognition Agreement (MRA) partner countries, reference can be made to the valid marketing authorization. **Any differences to the approved drug product should be justified.** ~~A statement should be provided that the active substance has the same quality as in the approved product.~~ The name of the ~~finished~~ **drug** product, the marketing authorisation number or its equivalent, the marketing authorisation holder and the country that granted the marketing authorisation should be given. (Reference is made to Table 1 of Regulation 536/2014)."	
122-124	4	**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 (WHO recommended). **Proposed change: "**Information concerning the nomenclature of the active substance (e.g. ~~proposed INN name,~~ pharmacopoeial name,…" ***Or*** Information concerning the nomenclature of the active substance (e.g. ~~proposed INN name,~~ **INN (if recommended),** pharmacopoeial name,…	Accepted.
139	1	**Comment:** Use of the word "adequately" in the sentence "The manufacturing process and process controls should be adequately described" is not helpful	Not accepted. It is the responsibility of the applicant to decide what is to be

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to clinical trial applicants. The guideline should state clearly what information will be considered adequate. If this is the information described in lines 140 – 154, this should be clearly stated. **Proposed change:** State clearly what information will be considered adequate.	considered 'adequate' for their particular product and stage of development.
142-148	4	**Comment:** It is understood that the agency defines 'relevant' process parameters as those related to safety. This emphasis on safety parameters is welcome and should clearly apply to both process parameters (input controls) and in-process tests (output controls) as the in-process controls (IPCs) defined in ICH Q11. It is considered appropriate to refine IPCs, and their criteria through development and language is requested for phase-appropriate criteria that may be based on prior knowledge. In line with reduction in duplication and to simplify post-approval amendments it is requested that the criteria for the listed safety-related parameters may be cross-referred to S.2.4. We request that the sentence that describes the IPC results being action limits or acceptance criteria be removed. The criteria for safety-related parameters should not be required to be reported in S.2.2 but recorded in S.2.4. Furthermore, we request that the	Party accepted. This section has been revised to include reference to the control strategy focussing on safety-relevant IPCs. It is considered that control limits based on a limited number of development batches are inherently preliminary and this has been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Sponsor has the flexibility to justify the type of control (action limit or acceptance criteria) or to record in the IMPD or monitor the results. Clarification is requested on the term 'recorded' as opposed to 'monitored' and 'reported'. It is not clear if the intention is for the results to be maintained internal to the Sponsor's QMS or reported in the IMPD. **Proposed change:** "A flow chart of all successive steps including relevant **in-process controls (**~~process parameters and in-process testing~~ as **defined in ICH Q11)** should be given. The ~~results of~~ in-process controls (IPCs) may be recorded as action limits or reported as preliminary acceptance criteria **and their t**esting should focus on safety relevant attributes ~~IPC~~. Acceptance criteria for **these IPCs** (e.g. ranges for process parameters of those steps involved in virus removal) should be available for manufacture of Ph I/II material **and may cross-refer to S.2.4**. For other, **non-safety-related** IPCs **that are described in the IMPD**, monitoring might be appropriate **and ranges do not need to be reported. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. At phase I/II, criteria may also take prior knowledge and experience with similar molecules and processes into consideration.**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed."	
142-148	5	**Comment:** The draft guideline states on lines 143-144 "The results of in-process controls (IPCs) may be recorded as action limits or reported as preliminary acceptance criteria". This sentence is confusing as it states that the results … "may be recorded" or "reported". Actual results of batches are typically not provided in S.2.2. It should be clarified if the statements "may be recorded" and "reported" are intended to instruct to provide in S.2.2 of the dossier, or a request to record internally for instance the batch record and maintained internally. If the intent is to provide in S.2.2 then more appropriate guidance would be required to provide the target operating ranges or target test values for relevant process parameters and in-process tests. Furthermore, the statement to record as action limits or report as preliminary acceptance criteria is also in conflict with line 146 which states "For other IPCs, monitoring might be appropriate". **Proposed change:** We would suggest rewording as follows:	Partly accepted. This section has been revised to include reference to the control strategy focussing on safety-relevant IPCs. It is considered that control limits based on a limited number of development batches are inherently preliminary and this has been clarified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A flow chart of all successive steps including relevant process parameters and in-process-testing should be given. ~~The results of in-process controls (IPCs) may be recorded as action limits or reported as preliminary acceptance criteria.~~ **The ranges for relevant operating parameters and in-process tests should be provided.** ~~Testing~~ **The control strategy** should focus on safety relevant IPCs and ~~A~~**a**cceptance criteria for critical steps (e.g. ranges for process parameters of those steps involved in virus removal) should be ~~available~~ **established** for manufacture of ~~Ph I/II material~~ **the clinical batches**. For other IPCs, monitoring might be appropriate. During development, as additional process knowledge is gained, further details of ~~IPCs~~ **the control strategy** should be provided and acceptance criteria reviewed.	
142	9	**Comments**: "Testing should focus on safety relevant IPC. Acceptance criteria for critical steps should be available for manufacture of Ph I/II material. For other IPCs, monitoring might be appropriate. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed". Request for clarification: In the specific case of IPC bioburden test, acceptance criteria would not be set for PhI/PhII. Results would be recorded, and a sterility test would be carried out on the end product. Sterility	Not accepted. Such clarifications are not to be provided in this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		test would be included in the specification. Acceptance criteria for the IPC test would be defined at a later stage, as product development and knowledge builds-on. Would this approach be acceptable and aligned with the content of the statement in line 142.	
144	7	**Comment:** Please clarify the following sentence by means of illustrative examples "Testing should focus on safety relevant IPC." **Proposed change:** " Testing should focus on safety relevant IPC ***(e.g.….)***."	Not accepted. The safety relevant IPCs will depend on the product. One example is already included in the text (i.e. IPCs relating to virus removal).
149 - 150	1	**Comment:** ACRO recommends that a clear distinction should be made between development batches and clinical batches and any differences in manufacturing should be discussed. **Proposed change:** Revise the statement to read "Batch(es) and scale should be defined, including information on any pooling of harvests or intermediates. A clear distinction should be made between development batches and clinical batches and any differences in manufacturing should be discussed."	Not accepted. This should not be discussed in this section but in S.2.6 and/or S.4.4, as appropriate.
151-154	4	**Comment:** It is agreed that reprocessing should only occur under exceptional (rare) circumstances that should be described in the IMPD. However, the term 'exceptional' is subjective and should be inherent to the justification for reprocessing. Also, the current	Not accepted. The text is sufficiently flexible to allow reprocessing on a case by case basis if appropriately justified. However, it is stressed that reprocessing is only acceptable under exceptional

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		text is considered to potentially be restrictive by listing a few more common examples of reprocessing; for example industry is increasing use of disposable bags in manufacturing processes. On rare occasion the integrity of a bag may be breeched. When the product can be justified as not having been compromised (e.g. bioburden) then it should be recognised as possible to allow reprocessing of that manufacturing step. Re-chromatography of defined steps may also be reprocessed, when suitably justified. It is important that any examples are understood as being examples and not as an exhaustive list of steps where reprocessing may take place. **Proposed change:** "~~Any reprocessing during manufacture of the active substance (e.g. filter integrity test failure) should be described and justified. Reprocessing could be considered in exceptional circumstances.~~ **Reprocessing is only allowable under the circumstances which are described and justified in the IMPD. Examples of reprocessing steps** ~~F~~**f**or biological products, **include but are not restricted to** ~~these situations are usually restricted to certain~~ re-filtration, ~~and~~ re-concentration ~~steps upon technical failure of equipment~~**, chromatography steps**~~ mechanical breakdown of a chromatography column)~~ **or use of disposable bags**."	circumstances.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
152-153	5	**Comment:** The use of the word “exceptional” is too strong. **Proposed change:** We would suggest revising as follows: Reprocessing couldd be considered in ~~exceptional~~ **certain** circumstances. For biological products, these situations are usually restricted to ~~certain~~ re-filtration and re-concentration…	Not accepted. Reprocessing is only acceptable under exceptional circumstances. The text is considered to be sufficiently clear.
164	9	**Comment**: this section indicates biologically sourced materials where A2 section discusses material of human or animal origin. Does biologically sourced material typically also include fermentation-derived products from yeast or bacterial origin? Are these excluded? Secondly, are medium substrates excluded from this analysis? Not clear to which level this applies (e.g. would this also apply to an enzyme produced via bacteria/yeast and used for cleaving in medium containing e.g. BSA)? **Proposed change**: *For all raw materials of biological origin (… <u>and with direct impact on the product</u>), …*	Partly accepted. “Biological” has been changed to “human or animal” to provide further clarification. However, the wording proposed is not appropriate since at early stages of development it may not be possible to conclude which raw materials have a direct impact on the product.
166-167	4	**Comment:** Summaries of adventitious agent testing should be sufficient in A2. Submission of original reports causes administrative burden and record keeping should be a GMP only topic.	Not accepted. The guideline refers to summaries which should be provided in Appendix A.2. Reference is made to the Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: In Section 2.3. Cell bank system, characterization and testing suggest to insert after last paragraph: **"A tabulated summary of the performed tests, acceptance criteria and results is usually sufficient and detailed reports do not need to be submitted."**	Products where further guidance is available.
175	4	**Comment:** It is possible for a product to enter clinical development before a MCB has been created. It is requested that a pre-MCB may be described in the IMPD in place of the final WCB. **Proposed change:** "**Unless otherwise justified, a** ~~A~~ MCB should be established prior to the initiation of phase I trials."	Not accepted. Standards for pre-MCBs are not defined. Reference is made to ICH Q5D.
177	1	**Comment:** The sentence "Information on the generation, qualification and storage of the cell banks is required" should be clarified as proposed below in order to avoid ambiguity. **Proposed change:** Reword the sentence to read "The following information on the generation, qualification and storage of the cell banks is required."	Not accepted. The request is not fully clear. Reference is made to ICH Q5B, where further guidance is available.
178-179	4	**Comment:** Cell culture performance can be impacted by many factors, including the production cell line. However, it is critical to recognize that a culture of any production cell line consists of a population of cells and absolute genetic homogeneity is not achievable given	Not accepted. It is acknowledge that clonality may be determined at substrate level in some cases. However in such cases it would not be difficult to demonstrate clonality also at the level of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the genomic plasticity inherent to immortalized mammalian cell lines. Furthermore, early toxicology may use material derived from intended, defined polyclonal populations. The BWP-proposed revision allows for this flexibility but there is concern on how the language will be interpreted by individual assessors. While it can be expected a production cell line derived and characterized as per ICH Q5D would be implemented moving toward late stage development/licensing, regulatory emphasis during development should be primarily placed on ensuring product quality of the material actually administered to patients relying on effective control strategies commensurate to product/process knowledge and understanding. **Proposed change:** "Clonality of the cell **substrate** should be addressed for mammalian cell lines." In addition, it is requested to move the sentence above to the section "Source, history and generation of the cell substrate" (line 173). Clonality is not determined at cell bank stage, it is determined during cell line generation.	cell line.
178-179	7	**Comment:** We understand the sentence "Clonality of the cell banks should be addressed for mammalian cell lines" to have the same intent as ICHQ5B which states	Not accepted. The proposal is not considered to provide sufficient

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that the criteria used to select the cell clone for production should be described in detail. We propose a rewording with a view to clarify the interpretation. **Proposed change:** ***The method used to generate clones should be described in sufficient detail to address clonality*** *for mammalian cell lines.*	information on the assurance of clonality.
185-187	4	**Comment**: Considering no critical change in the process manufacturing the introduction of a new WCB should be justified according to ICH Q5D, as well as a QC testing on the active substance. This guideline should leave the flexibility for using a protocol to introduce a new WCB implementation during clinical study to avoid a substantial amendment. **Proposed change:** Add to line 187 **"When the tests and criteria are provided to characterise a future, replacement WCB and no impact to product quality is subsequently concluded, then introduction of the new WCB should not be considered a substantial change."**	Not accepted. The proposal outlines a very special event which is not expected to occur frequently in an ongoing CT. It is considered too detailed to include this in the guideline. This is applicable for MAA.
185	5	**Comment:** The presence of "(new)" creates uncertainties if this is also required for a new batch of WCB. The requirements should only be applicable to the introduction of the first WCB in the product	Partly accepted. The reference to 'new' has been removed. The reference to 'first' introduction of the WCB into the manufacturing process is not endorsed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		development. **Proposed change:** We would suggest revising as follows: As for any process change, the introduction of a ~~(new)~~ WCB may potentially impact the quality profile of the active substance, and comparability should be considered **when use of WCBs is first introduced into the manufacturing process** (see section S.2.6. Manufacturing process development).	
185	7	**Comment:** "As for any process change, the introduction of a (new) WCB may potentially impact on the quality profile of the active substance and comparability should be considered" In order to ensure a common interpretation, we encourage EMA to reword this sentence clarifying that the (new) WCB is derived from the same MCB. **Proposed change:** "As for any process change, the introduction of a (new) WCB ***derived from the same MCB may potentially impact*** on the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development)."	Not accepted. The proposal does not add clarity.
191	1	**Comment:** The sentence "Any available data on cell substrate stability should be provided" implies that such data will never be a mandatory requirement for	Not accepted. The data that is available should be submitted. The text is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		trial approval. If this is so, it should be stated clearly or the circumstances in which cell substrate stability will be required should be described. **Proposed change:** Make clear that cell substrate stability data should be submitted if available, but are not mandatory (except in certain circumstances that should be described in the guideline).	considered sufficiently clear.
193-196	4	**Comment:** Section S.2.4 should summarise the safety-relevant control parameters. To reduce repetition and ease post-approval maintenance S.2.2 may cross-refer to S.2.4 for the criteria which may be action limits or acceptance criteria. **Proposed change:** None.	Accepted.
197	3	**Comment:** Return to original text as for early clinical phases validation may not be available **Proposed change:** S.2.5. Process validation and/or evaluation	Not accepted. Process evaluation is considered sufficiently covered by the term process validation. Please refer to the "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014). Section P.3.5 has been amended accordingly.
197	4	**Comment:** Typographical - Assume removal of 'and/or evaluation' from the title for section S.2.4 was a typographical error, as this language was not removed from the equivalent drug product section,	Not accepted. Process evaluation is considered sufficiently covered by the term process validation. Please refer to the "Guideline on process validation for the manufacture of biotechnology-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Line 469. **Proposed change:** Re-insert wording, 'S.2.5. Process validation **and /or evaluation**'	derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014). Section P.3.5 has been amended accordingly.
197	5	**Comment:** The heading for S.2.5 is not aligned with CTD headings. **Proposed change:** We would suggest revising as follows: S.2.5. Process validation **and/or evaluation**	Not accepted. Process evaluation is considered sufficiently covered by the term process validation. Please refer to the "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014). Section P.3.5 has been amended accordingly.
197-201	9	**Comment:** It is clear that process data will be collected during development and clinical development, but it is not expected that the process is fully validated before phase 3, usually this is done with phase 3 CTM batches. **Proposed changes:** 1 - Change heading back to *S.2.5 Process validation <u>and/or evaluation</u>*. This allows the applicant to evaluate the collected data. 2 - Process ~~validation~~ data should be collected …	Not accepted. Process evaluation is considered sufficiently covered by the term process validation. Please refer to the "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014). Section P.3.5 has been amended accordingly.
198	3	**Comment:** Return to original text as for early clinical phases validation may not be available	Not accepted. Process evaluation is considered sufficiently covered by the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Process validation / evaluation data should be collected throughout development, although they are not required to be submitted in the IMPD.	term process validation. Please refer to the "Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission" (EMA/CHMP/BWP/187338/2014). Section P.3.5 has been amended accordingly.
197 - 199	1	**Comment:** ACRO concurs that, with the noted exception of manufacturing steps to remove or inactivate viral contaminants, information on process validation and/or evaluation is not applicable for a risk assessment of active substances intended for clinical trial use, and welcomes this recognition.	The comment is noted.
202-211	9	**Comment:** In case of prior knowledge including platform technologies, e.g. when cell bank, cell culture, process etc. are similar/equivalent to previous approved IMP, reference to those approved documents could be supportive. **Proposed change:** To be added: 'Knowledge about platform technologies, when earlier approved or submitted in an IMPD, can be referenced'.	Not accepted. The existing wording is sufficiently flexible to include use of prior knowledge if relevant and justified. It is currently not feasible to refer to previously submitted IMPDs.
210 - 211	1	**Comment:** ACRO recommends that the proposed justification should be based on a risk-based assessment. **Proposed change:** Revise the statement to read "If process changes are made to steps involved in viral	Not accepted. Does not add clarity. The existing wording is sufficiently flexible to include an appropriate risk-based justification if appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clearance, a risk-based justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable."	
213 - 215	1	**Comment:** ACRO recommends clarifying that the comparability exercise should follow risk-based principles, using pre-defined criteria to establish comparability. **Proposed change:** Revise the statement to read: "Depending on the consequences of the change introduced and the stage of development, a risk-based comparability exercise may be necessary to demonstrate that the change would not adversely impact the quality of the active substance. The comparability exercise should be based on pre-defined criteria."	Not accepted. Does not add clarity.
215-217	4	**Comment:** Before dose finding, safety is assessed but not efficacy. During early phases, the comparability exercise should focus on safety. During later phases the comparability exercise should assess both safety and efficacy. Phase-appropriate guidance is proposed. **Proposed change:** "**In early phases** the main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that it will not ~~impact on …. or~~ raise any concern regarding safety of the patients included	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in the clinical trial. **In addition, for later phases, it should be assessed if the post-change material could** impact the efficacy of the IMP**.**"	
233-234	4	**Comment:** Reference to prior knowledge or literature could be used when justified e.g. C-terminal lysine or other modification where a clear understanding of safety is available and could be used for justification **Proposed change:** Reference to the literature data only is not acceptable **unless supported and justified by prior knowledge from similar molecules for modifications where there is no safety concern e.g. C-terminal lysine.**	Accepted.
234 - 235	1	**Comment:** Use of the word "adequate" in the sentence "Adequate characterisation should be performed in the development phase prior to phase I and, where necessary, following significant process changes" is not helpful to clinical trial applicants. The guideline should state clearly what information will be considered adequate. If this is the information described in lines 236 - 242, this should be clearly stated. **Proposed change:** State clearly what information will be considered adequate.	Not accepted. It is the responsibility of the applicant to decide what is to be considered 'adequate characterisation' for their particular product. Leaving the sentence as is also allows sufficient flexibility to adapt depending on the product type. Reference is also made to the "Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products" (CHMP/SWP/28367/07).
248-249	4	**Comment:** During early development, data specific to process-related impurity clearance may not be complete. When suitably justified, it should be possible	Not accepted. The existing wording is sufficiently flexible to include use of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to extrapolate clearance data from highly similar processes to manufacture related products, e.g. monoclonal antibodies. For the first in human studies, the highest clinical dose is often not known and still to be defined. **Proposed change:** "Quantitative information on impurities should be provided including maximum amount for the highest **anticipated** clinical dose. **Prior knowledge and experience for process-related impurities may be used to predict clearance for similar products and highly similar process steps and control (e.g. leached protein A, residual DNA).** For certain process-related impurities (e.g. antifoam agents), an estimation of clearance may be justified."	prior knowledge if relevant and justified. Inclusion of the word 'anticipated' is not considered appropriate as the maximum dose must be specified for each clinical trial.
253 - 255	1	**Comment:** The sentence "When process validation data are incomplete, the quality attributes used to control the active substance are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes" is confusing relative to the statement in lines 197 – 199 that process validation data are not required to be submitted. Process validation data that exist but are not submitted will not be known to the reviewing competent authorities, who, as a result, may wrongly consider the quality attributes used to control the	Not accepted. It is said in the guideline that quality attributes controlled throughout the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		active substance to be inadequate. **Proposed change:** The guideline should describe how clinical trial applicants should explain the use of quality attributes to control the active substance in the absence of submitted process validation data.	
255 - 257	1	**Comment:** ACRO recommends that quality attributes not included in the specification should be pre-defined and justified. **Proposed change:** The statement should be revised to read: "Therefore the quality attributes controlled throughout the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set. Quality attributes not included in the specification should be pre-defined and justified."	Not accepted. It is not considered feasible to pre-define and justify quality attributes not included in the specification.
259-272	4	**Comment:** Whilst agreed that for many of the attributes included in the specification, acceptance criteria should be established as early as possible, for some parameters this is not possible at early development based on data. As acknowledged in line 268 – 272 only limited amount of batches are available during early development for inclusion into acceptance criteria setting and thus for specific product characteristics such as purity and	Not accepted. As purity is linked to safety it is essential to include acceptance criteria. In early development, it is acknowledged that the acceptance ranges may be wide.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product-related variants results can only be reported. Furthermore, the statement in line 261 – 262 is contradictory to the statement in line 268 – 272: "Product characteristics that are not completely defined at a certain stage of development e.g. glycosylation, or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits". The proposed changes would improve the guideline's consistency. **Proposed change: Line 261-262:** "Tests and defined acceptance criteria are mandatory for quantity~~,~~ **and** identity ~~and purity and~~ **for which** a limit of 'record' or 'report results' will not be acceptable."	
261-262	5	**Comment:** "quantity" should be replaced by "potency" as the quantity of API produced is not included in S.4.1. The statement that "a limit of 'record' or 'report results' will not be acceptable" is appropriate for certain tests. However, there will be some early studies where it is still preferable to indicate that tests for purity are performed as part of release but that it is too early to assign realistic limits. **Proposed change:** We would suggest revising as	Not accepted. Quantity is an essential parameter. The proposal to replace it by potency is not understood. As potency assays frequently exhibit a relatively high variability they are not considered suitable to quantify the substance

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		follows: Tests and defined acceptance criteria are mandatory for ~~quantity~~ **potency**, identity and purity and a limit of 'record' or 'report results' **is** ~~will~~ not ~~be~~ acceptable **without appropriate justification**.	
261-263	7	**Comment:** In early development with limited number of batches manufactured, it will be difficult to establish scientifically justified acceptance criteria for some aspects. Note that lines 268-272 below appear to be somewhat contradictory to lines 261-263 with regard to purity aspects. **Proposed change:** "Tests and defined acceptance criteria are mandatory for quantity and identity and a limit of 'record' or 'report results' will not be acceptable for parameters ***where sufficient data are available to establish relevant criteria***."	Not accepted. As purity is linked to safety it is essential to include acceptance criteria. In early development, it is acknowledged that the acceptance ranges may be wide.
262	6	**Comment:** We request clarification to be added as to whether this applies to all phases of trial, or only later phase trials. There may be insufficient manufacturing experience accumulated to determine numerical criteria for some quality attributes for some products in the early stage of development. **Comment:** If it is to apply to all phases of trial, please add clarification to the guideline to confirm this. **Comment:** We request that the word "will" is	Not accepted. From the wording it is clear that this applies to all phases of clinical trials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		changed, as it will not be clear once the guideline is finalised when this would be applicable. The wording could be changed to "is not accepted...". **Proposed change:** "a limit of 'record' or 'report results' is not accepted...".	Not accepted
262	9	**Comment:** .. *Limit of 'record' or 'report results' will not be acceptable* …. has been added to the guideline. In early phases of the development, results are sometimes used for monitoring, trending or setting the specifications. **Proposed change:** .. and a limit of 'record' or 'report results' <u>will need to be justified.</u>	Not accepted. As the given parameters are linked to safety it is essential to include acceptance criteria for all clinical trials. In early development, it is acknowledged that the acceptance ranges may be wide.
265-266	4	**Comment:** In early phase there may only one batch to set the limit and in phase II there may also be too few lots to determine a viable specification and thereby not enabling reasonable consideration for the capability of the manufacturing process. **Proposed change:** To add: **"In phase I/II there may be few lots on which to base the specification (and phase III for biosimilar investigational products). A preliminary specification may be derived using prior knowledge for similar products and/or risk-based assessment of the product quality attributes**."	Not accepted. Not accepted. For quality attributes linked to safety it is essential to include acceptance criteria for all clinical trials. In early development, it is acknowledged that the acceptance ranges may be wide. If available an applicant can use prior knowledge for setting specifications probably leading to tighter specifications in early phases.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
265 - 267	1	**Comment:** ACRO recommends that any differences in the manufacturing process between development batches, clinical batches and non-clinical batches should be summarized and explained. **Proposed change:** Revise the statement to read: "As the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development. Any differences in the manufacturing process between development batches, clinical batches and non-clinical batches should be summarized and explained."	Not accepted. The manufacturing process should not be discussed in this section but in S.2.6 or S.4.4, as appropriate.
268-270	4	**Comment:** Charge heterogeneity is not specifically addressed in the specifications section. Although the charge heterogeneity profile i.e. peak pattern is often available at early stages of development, data are limited. Therefore, at the early stages of product development, it should be appropriate to include such tests on the specification without predefined limits. **Proposed change:** "Product characteristics that are not completely defined at a certain stage of development **(**e.g. glycosylation, **charge heterogeneity)** or for which the available data is too limited to establish relevant acceptance criteria, should	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		also be recorded."	
268-272	7	**Comment:** Please see above comments with regard to purity aspects where sufficient batch data will be needed to set suitable acceptance criteria. **Proposed change:** "Product characteristics that are not completely defined at a certain stage of development (e.g. glycosylation***, charge variants***) or for which the available data are too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. The results should be reported in the Batch Analyses section (S.4.4)."	Accepted.
270-271	5	**Comment:** 'Record' or 'report results' should be acceptable in Phase I and Phase II trials for non-critical parameters when data is limited. It is important that sections S.4.1 and P.5.1 are aligned (see below comments for lines 511-514). **Proposed change:** We would suggest revising as follows: As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. **In such cases, a limit of 'record' or 'report results' is acceptable.**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
280 - 281	1	**Comment:** ACRO considers that it is important for evaluation purposes that the controls used in non-compendial analytical procedures are presented. **Proposed change:** Revise the statement to read " A brief description of all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided, highlighting controls used in the analysis."	Accepted.
288-292	4	**Comment:** Sentence about validation parameters is now redundant with the added clarity about how/when to present validation information. **Proposed change:** ~~The acceptance limits (e.g. acceptance limits for the determination of the 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 a tabulated form.~~	Not accepted. The text is not considered redundant and should be kept for clarity.
288	7	**Comment:** "For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed." To foster common interpretation of the guideline, we suggest to explicitly refer to the suitability of analytical methods used for the active substance. Excipients may be present however would have no relevance for the	Not accepted. Also for the testing of certain DS intermediates suitability of the analytical methods needs to be demonstrated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		safety or efficacy of the IMP in the clinical trial. **Proposed change:** "For phase I and II clinical trials, the suitability of the analytical methods used ***for the active substance*** should be confirmed."	
294-295	7	**Comment:** "Information for phase III clinical trials Validation of the analytical methods used for release and stability testing is expected." To foster common interpretation of the guideline, we suggest to explicitly refer to the validation of analytical methods used for release and stability testing for the active substance. Excipients may be present however would have no relevance for the safety or efficacy of the IMP in the clinical trial. **Proposed change:** "Information for phase III clinical trials. Validation of the analytical methods used for release and stability testing ***for the active substance in the drug product*** is expected."	Not accepted. Also for the testing of certain DS intermediates suitability of the analytical methods needs to be demonstrated.
295-297	4	**Comment:** Formal validation, including robustness supporting analysis at multiple sites, may not be complete at this phase of development. Method qualification should be sufficient at this phase of development. **Proposed change:** "**The suitability** ~~Validation~~ of the analytical methods used for release and stability testing **should be demonstrated** ~~is~~	Not accepted. For phase III studies validation of the analytical methods used for release and stability testing should be provided. By the end of phase III full method validation must be completed, including confirmation of robustness.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~expected~~ **according to ICH Q2R1.** A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate **for the phase of development**)."	
295	5	**Comment:** We noted the change of wording from "suitability" to "validation" of the analytical methods used…. This could be interpreted that complete ICH method validation is needed to support initiation of Phase III clinical trials. It is recommended that the original wording "suitability" be retained since some ICH validation parameters (e.g. robustness) might not be in place at the start of Phase III trials. Full ICH method validation may be completed concurrently with Phase III trials to support the MA submission. **Proposed change:** We would suggest revising as follows: ~~Validation~~ **Suitability** of the analytical methods used for release and stability testing is expected.	Not accepted. For phase III studies validation of the analytical methods used for release and stability testing should be provided. By the end of phase III full method validation must be completed, including confirmation of robustness.
296	4	**Comment:** Typographical **Proposed change:** change "…. ~~e~~**c**arried …."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
303-306 and 533-535	4	**Comment:** Data representative of the material used in the trial is provided in the IMPD. The purpose of the release specification and the final drug product EU QP Batch Release Process is intended to assure that the product is of the intended quality. To provide batch data for lots known in advance to be used for a given Study would be extremely challenging to Sponsors managing global trials for a given product. There can be a long lead time between Study approval and Study initiation in the clinic as approvals are sought, sites set-up etc. such that batches reported in an IMPD may be exhausted by time of study start. Furthermore, studies may last for several years and it would not be desirable to maintain the batch data for lots to be used in the study. This text may therefore lead to additional burden on sponsors and national competent authorities and adds little value when it is considered that the IMPD describes how future batches will be controlled. Therefore, the EMA is requested to include the suggested condition that actual batches to be used in the study need only be provided in S.4.4 if not representative of the prior analyses. **Proposed change:** "For early phase clinical trials where only a limited number of batches of active substance have been manufactured, test results from	Not accepted. For early phase clinical trials where usually only a limited number of batches of active substance have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial. This adds value as normally acceptance criteria are wide and a number of quality attributes are don't have acceptance criteria and are only monitored (report results)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD**, if different from representative batches provided in the IMPD. When analytical data for batches representative of those batches to be used in the clinical study are presented, no further maintenance of this section is required"**	
309 - 310	1	**Comment:** ACRO recommends that any manufacturing process differences between batches should also be identified. **Proposed change:** Revise the statement to read: "The manufacturing process used for each batch and any differences in these processes should be identified."	Accepted.
311-313 and 541-543	4	**Comment:** These statements might lead to the (undesired) interpretation that a substantial amendment is required to add release data (once available) from a batch mentioned in the Q-IMPD that is not yet manufactured at the time of submission of the dossier. Additional clarity has been proposed and is located for Lines 303-306 and Lines 533-535. An IMPD can be cross referred to different clinical trials for which it would be difficult to anticipate the supply. As all the clinical batches have to be in compliance with suitable release specification, there is not any	Partly accepted. It is agreed to delete "In any case". The remainder of the proposal is not considered to make the guidance any clearer.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		added value to provide such statement in "In any case ...." for early clinical phase. We are of the opinion that the Guidance text provided in the initial version of this guideline is sufficient and clearly states that at early stages data of all batches manufactured have to be provided and only a number of representative batch data at later stages. The Q-IMPD should support and reflect current clinical trials. **Proposed changes:** **Lines 311-313**; "~~In any case a~~ **A** statement should be included whether the batch analyses data presented are ~~from~~ **representative of** the batches that will be used in the clinical trial,~~ or whether additional batches not yet manufactured at time of submission of the Investigation Medicinal Product Dossier (IMPD) might be use~~ otherwise, the batch data should be provided." **Lines 541-543**; "~~In any case a~~ **A** statement should be included whether the batch analyses data presented are ~~from~~ **representative of** the batches that will be used in the clinical trial,~~ or whether additional batches not yet manufactured at time of submission of the Investigation Medicinal Product Dossier (IMPD) might be use~~ otherwise, the batch data should be provided."	
314 - 326	1	**Comment:** As above (comment on lines 253 – 255).	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: The guideline should describe how clinical trial applicants should explain the use of quality attributes in the specification and acceptance criteria to control the active substance in the absence of submitted process validation data.	As above outcome on lines 253-255.
319-320	4	**Comment:** It is important to recognise that during development that data supporting the proposed specifications may be limited on the IMP and in such cases wider limits can be set if appropriately justified. **Proposed change:** Add **"In phase I/II there may be few lots on which to base the specification (and phase III for biosimilar investigational products). A preliminary specification may be derived using prior knowledge for similar products and/or risk-based assessment of the product quality attributes."**	Not accepted. The existing wording is sufficiently flexible to include use of prior knowledge if relevant and justified.
331 - 333	1	**Comment:** Use of the words "adequate" and "adequately" in the sentence "The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be adequately described" is not helpful to clinical trial applicants. The guideline should state clearly what information will be considered adequate. **Proposed change:** State clearly what information will be considered adequate.	Not accepted. The description of the analytical methods used depends on the stage of development and it is the responsibility of the applicant to decide what is to be considered 'adequate' for their particular product and stage of development. The same principles as for the description of methods used for characterisation of the IMP are applicable.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
338-339	4	**Comment:** A definition for 'primary reference material' is requested. Is it correct to understand that the term refers to a standard produced by the same manufacturing process as the substance first use in human? **Proposed change:** None	Not accepted. Primary reference material is a common term. It is an appropriately characterised material prepared from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. For new molecular entities, it is unlikely that an international or national standard will be available. Manufacturer should establish an appropriately characterized in-house primary reference material, prepared from lot(s) representative of clinical materials.
338-339	7	**Comment:** "If available, an international or *Ph.Eur.* standard should be used as primary reference material. Each in-house working standard should be qualified against this primary reference material." The development of standards and reference materials is an on-going and continuous process. It is not uncommon for the off-patent sector to see those standards made available during the development process. With the current wording, it is likely that the release of a newly developed reference standard will affect the clinical trial programme (delays in timelines) of	Not accepted. If an official standard is available it should be used wherever possible. Any deviations from this guidance should be appropriately justified in the dossier and would be subject to assessment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ongoing developments. It is therefore important to foresee the possibility for an applicant to justify using risk-based approaches the continued use of in house standards in cases where an international or Ph.Eur. standard that was not available for qualification of the in-house reference material happened to be released. We encourage a pragmatic approach consisting in agreeing on the implementation or transition period by the end of which the necessary qualification work against the primary standard would have to be performed. As referenced in the WHO draft guideline on Good regulatory practices (currently under public consultation - WHO Working Document QAS/16.686-Good regulatory practices: guidelines for national regulatory authorities for medical products), "*Medical product regulations must continue to evolve to reflect advances in science, standards of care and technology. Nevertheless, regulatory requirements and their application and implementation must be consistent and predictable over time in order to allow all parties to make reasonably informed decisions on investments, resources and steps to ensure continued compliance. When changes are necessary, clearly stipulated measures and transition periods should be established.*" **Proposed change:** If ***already*** available ***for more***	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		than 2 years, an international or Ph.Eur. standard should be used as primary reference material. Each in-house working standard should be qualified against this primary reference material. ***In cases where an international or Ph.Eur. standard was made available for less than 2 years, the necessary qualification work should be completed within 1 year of the completion of the clinical trial or as part of the marketing authorisation submission.***	
338-343	4	**Comment:** The requirement for monitoring of stability of the reference material is a GMP requirement and does not need to be documented in the Q-IMPD during development. It will be documented for MAA. Our current understanding is that the primary reference material should be representative of the commercial material. Thus, for early development projects a primary reference material for a two-tiered system is not easily contrivable. Instead, a one-tiered system with interim primary reference is used as in-house working standard until availability of representative commercial material. Proposed change: Please replace the last sentence with: "The stability of the reference material should be monitored **but is not expected to be reported in the IMPD but managed in the Quality**	Partly accepted. Monitoring the stability of the reference material can be handled in the Quality System of the company.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Management System. **During development it is acceptable, that an interim primary reference is used as in-house working standard until material representative of the commercial product is available."**	
341-342	7	**Comment:** According to the ICH Q6B the following was determined in the section of ***2.2.1 Reference standards and reference materials:*** "For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material." The draft IMPD guideline in lines 341-342 says that "if an international or Ph. Eur. standard is not available, an in-house standard should be established during development as primary reference material." There is a discrepancy in the requirement laid out in the present draft IMPD guideline and ICH Q6B.	Not accepted. The guidance proposed is not considered to contradict ICH Q6B. It is acknowledged that ICH Q6B provides more detailed guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please align requirements in the present draft with the ICH Q6B.	
344-346	2	**Comment:** It is not clear for the possible interactions between the active substance and the immediate packaging, what is the extend of information that should be included in the quality documentation of IMPD in relation with phase I and phase II, III. If a tabulated protocol of the study will be satisfactory for the phase I, and then later for phase II and III providing the tabulated results would fulfil the requirements, these details should be stated within this paragraph (S.6.-Container closure system).	Not accepted. The current wording allows for some flexibility to adapt expectations to the specific product and container closure type and to the stage of development.
345 - 346	1	**Comment:** ACRO recommends that more guidance should be provided here as some Member State regulatory authorities accept a general description of the container/closure system whereas others routinely ask for sponsors to confirm that the components of the container/closure system comply with applicable Ph.Eur monographs, EC Directives and EC Regulations. For example, recent examples of questions received by ACRO member companies during evaluation of clinical trial applications are: - "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	Not accepted. The current wording allows for some flexibility to adapt expectations to the specific product and container closure type and to the stage of development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		substance is packaged in a container closure system that meets the corresponding relevant standards in force (i. e. Directives, Eur. Ph. etc.)." **Proposed change:** Clarify in more detail the level of information required on the container/closure system.	
358-360	2	**Comment:** Stress conditions studies are also recommended as to understand the degradation profile of the drug product. Since this is not a mandatory request, then we understand that the presentation within IMPD quality documentation of the stress study protocol and further stress study results will be accepted at any stage of development unless otherwise clear instruction will be included in the present guideline.	Accepted.
361	7	**Comment:** "The stability-indicating properties of the analytical methods" is not clear in this draft guideline. We propose 2 alternative wording which would enable a common interpretation of the requirements. **Proposed change:** "The stability-indicating ~~***properties of the analytical***~~ methods included in the stability protocol should be discussed to provide assurance that changes in the purity / impurity profile and potency of the active substance would be detected."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		or please revert to the previous version of this sentence from the Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials- 15 March 2012 EMA/CHMP/BWP/534898/2008: **"Stability-indicating methods should be included in this stability protocol to provide assurance that changes in the purity / impurity profile and potency of the active substance would be detected. A potency assay should be included in the protocol, unless otherwise justified."**	
361-363	4	**Comment:** Stability-indicating properties of analytical methods may be described in S.4.3, as described in ICH Q2R1. If such data are available and described in S.4.3 then it would be appropriate to refer to that section. **Proposed change:** Add: "The stability-indicating properties of the analytical methods included in the stability protocol should be discussed**, or cross-reference to S.4.3 made,** to provide assurance that changes in …."	Accepted.
361-364	9	**Comment:** It is mentioned that the *stability-indicating properties <u>of the analytical methods</u>* included in the stability protocol should be discussed […]. Stability-	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		indicating properties of the active substance should be addressed instead. **Proposed change***: 'The analytical methods for the stability-indicating properties of the active substance included in the stability protocol should be discussed […].'*	
383-399	9	**Comment:** It is explicitly mentioned that the extension [of the shelf-life] beyond the intended long-term stability study is not acceptable. So for example; when the shelf life is set at 2 years; it cannot be extended beyond the 2 years; also not with additional stability data? The text should be restructured for clarity sake. **Proposed changes:** 1- … *The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by available real-time stability data obtained with the representative batch/ (es). However, extension of the shelf life beyond the intended duration of the long-term stability studies is not acceptable.* 2 -The section starting with *Where extensions of the shelf-life are planned … On shelf-life extension by way of substantial amendment, see section 4.)* (i.e., lines 396 – 399) should follow the above section promptly and the section starting with *Prior knowledge including*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		platform technologies (i.e. lines 393-395) should only follow thereafter.	
390-391 & 644-645	10	**Comment:** It seems to have a wording inconsistency between the statement dealing with shelf-life extension rules within the document Line 390-391: The maximum shelf-life after the extension should not be more than double**, or** more than **twelve months longer than the period covered by stability data** obtained with representative batch(es). Vs Line 644-645: However, shelf-life extension based on the agreed protocol **is** typically **not** considered as substantial amendment if: each additional extension of the shelf-life **is not** more than double **or** more than **twelve months longer than the approved shelf-life.** Indeed, for a theoretical case of an IMP with a 24 months shelf life established based on a real time stability data up to a 12 months timepoints a) it would be possible to consider a shelf life extension to a 36months period following rules described in lines 644-645 based on real time stability data up to a 18 months timepoint b) while only a shelf life extension to a 30 months period maximum could be considered based on real time stability data up to a 18 months	Partly accepted. Concordant statements on shelf lie extension are included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		timepoint following rules described in lines 390-391. Lastly, the use of a double negative verb form and the use of the conjunction “or” in lines 644-645 may be misleading for some readers as they could interpret it as shelf life extension is not a substantial amendment if it fills one or the other criterion which may be the opposite of lines 390-391 requesting to meet the 2 conditions. **Proposed change:** a) If both criterion need to be filled and 2nd criterion is based on real time stability data Line 644-645: However, shelf-life extension based on the agreed protocol is typically not considered as substantial amendment if: each additional extension of the shelf-life is not more than double ~~or~~ **and extension of the shelf-life is not** more than twelve months longer than **the period covered by stability data obtained with representative batch(es)** ~~the approved shelf-life~~. b) If both criterion need to be filled and 2nd criterion is based on approved shelf life Line 390-391: The maximum shelf-life after the extension should not be more than double~~, or~~ **and it should not be** more than twelve months longer than **the approved shelf-life** ~~the period covered by~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~stability data obtained with representative batch(es)~~.	
399	5	**Comment:** Reference should be made to section 6 (lines 642-650) as additional sections have been included in the guideline. **Proposed change:** We would suggest revising as follows: On shelf-life extension by way of substantial amendment, see ~~section 4~~ **section 6**.	Accepted.
410-411	4	**Comment:** Container closure is repeated in different sections of the IMPD. Suggest to cross-reference to P7 when appropriate. **Proposed change:** Section P.1 Suggest to add to last bullet: **"A reference to P.7, container closure system should usually be sufficient"**	Partially accepted. A brief description is still required in this section.
410-411	8	**Comment:** *In section P1, the following information should be provided: "A brief description of the type of container and closure used for the dosage form and for any accompanying reconstitution diluent and* ***devices****, if applicable."* It should be clarified if the concerned devices in this sentence are only the ones used for the reconstitution or all devices that may be provided in the therapeutic unit (for example: syringe or infusion system used for the administration).	Not accepted. It is not feasible to cover all possible scenarios here in view of the multitude of devices available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It should be also clarified what is expected here: either a brief description of the container closure of the device or a brief description of the device.	
416	4	**Comment:** 'For products requiring additional preparation…' Assume this affects only IMPs, not AMPs, as AMPs are not mentioned in scope section 1.2? **Proposed change:** 'For **IMPs** requiring additional preparation…'	Not accepted. AMPs are within the scope of the guideline.
428-429	1	**Comment:** ACRO recommends clarifying that the comparability exercise should follow risk-based principles, using pre-defined criteria to establish comparability. **Proposed change:** Revise the statement to read: "An appropriate comparability exercise with supporting risk-based assessment should support significant changes, e.g. formulation changes."	Not accepted. A supporting risk-based assessment is not considered sufficient. The analytical comparability exercise should be documented.
439-440	4	**Comment:** It is requested to provide guidance on the hospital exemption. **Proposed change:** In accordance with draft guidance EMA/CHMP/QWP834816/2015 add the following between Lines 439-440: **"When packaging and or labelling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at that institution, and**	Not accepted. Providing detailed guidance in relation to the hospital exemption is not considered to be within the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		where an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the regulation 536/2014 applies, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place."	
444-448	4	**Comment:** It is understood that the agency defines 'relevant' process parameters as those related to safety. This emphasis on safety parameters is welcome and should clearly apply to both process parameters (input controls) and in-process tests (output controls) as the IPCs defined in ICH Q11. It is requested to be clear that in-process controls means 'in-process tests' and 'process parameters'. In line with reduction in duplication and to simplify post-approval amendments it is requested that the criteria for the listed safety-related parameters may be cross-referred to P.3.4. It is considered appropriate to refine process parameters and IPCs, and their criteria through development and language is requested for phase-appropriate criteria. **Proposed change: "**A flow chart showing all steps of the manufacturing process, including relevant **in-process controls (IPCs)** ~~process parameters and in-process tests~~ should be provided accompanied by a	Partly accepted. Wording was changed to add more clarity. See also S 2.4

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		brief process description. The ~~results of~~ in-process ~~tests~~ **controls (IPCs)** may be recorded as action limits or reported as preliminary acceptance criteria **and their testing should focus on safety relevant attributes** ~~IPC~~. Acceptance criteria for **these IPCs may cross-refer to P.3.4**. During development, as process knowledge is gained, further detail of ~~process parameters and in-process testing~~**IPCs and the criteria should be provided and acceptance criteria reviewed."**	
444-446	5	**Comment:** "relevant process parameters" should be included in the process narrative rather than in the flow chart (line 444). The sentence on lines 445-446 is confusing as it states that the results … "may be recorded" … or "reported". Actual results of batches are typically not provided in P.3.3. It should be clarified if the statement "may be recorded" is intended to instruct to provide actual results in P.3.3 of the dossier or requesting to record internally for instance the batch record and maintained internally. If the intent is to provide in P.3.3, it would be more appropriate to provide the range, action limit or preliminary acceptance criteria for relevant in-process tests. **Proposed change:** We would suggest revising as follows:	Not accepted. The relevant process parameters should be maintained in the flow chart.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A flow chart showing all steps of the manufacturing process, including ~~relevant process parameters and~~ in-process tests, should be provided accompanied by a brief process description. The ~~results of in-process tests may be recorded as~~ **ranges for** action limit~~s~~ or ~~reported as~~ preliminary acceptance criteria **should be provided for relevant in-process tests**.	
453-454	4	**Comment:** The reference is not fully complete as this guideline replaces the note for guidance on process validation (CPMP/QWP/848/96, EMEA/CVMP/598/99) **including annex II – non-standard** processes (CPMP/QWP/2054/03). **Proposed change:** "See Guideline on process validation for finished products - information and data to be provided in regulatory submissions ~~Annex II: Non-Standard Processes~~ EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1"	Accepted.
459-460	2	**Comment:** It is not clear when the holding times study protocol and study results should be included in the IMPD quality documentation.	Not accepted. The current text is considered to be sufficiently clear: If holding times are foreseen for process intermediates, duration and storage conditions should be provided and justified by data in terms of physicochemical, biological and microbiological properties.
461-466	4	**Comment:** Given industry efforts to justify use of volumes less than 100 mL and the lack of scientific	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		rationale for 100 mL, it is requested that the EMA relaxes the language used for the bioburden test volume to allow justification of smaller volumes using risk-based approaches. In support of this request the recently published EBE cross-industry position paper on the risk-based approach to bioburden is provided. **Proposed change:** "For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable~~**., depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If availability of the formulated medicinal product is limited, a pre-filtration/filtration**~~ **Test** volume**s** of less than 100 ml may be tested if justified **through risk assessment and holistic evaluation of the manufacturing process with respect to bioburden. The risk assessment should consider bioburden levels prior to filtration and potential for bioburden breach. Risks may be further mitigated through the use of a pre-sterile filtration, bioburden reduction filter and a qualified hold time from this filtration to end of filling**."	The text is changed to allow for testing volumes less than 100ml The proposed additional text is considered too detailed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
461-466	7	**Comment:** Given the industry interest in justifying a lower sample volume and the number of risk-based studies available in the literature, we suggest to delete the conditions whereby a lower sample volume may be justified. **Proposed change:** "For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable, ~~***depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If availability of the formulated medicinal product is limited, a***~~ A pre-filtration/filtration volume of less than 100 ml may be tested if justified."	Accepted.
467-468	4	**Comment:** The description and justification of reprocessing steps should be located in P.3.3. **Proposed change:** Please relocate this statement to P.3.3**: "Reprocessing may be acceptable for particular manufacturing steps (e.g. re-filtration) only if the steps are adequately described and appropriately justified."**	Accepted.
470-473	2	**Comment:** In case of aseptic processing and lyophilisation the "state of validation" should be	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clarified by the extend of information expected in relation with the phase I and II, III (validation protocol only; or when results are expected?). The validation data requested in case of sterilising process should be clarified in relation with the type of sterilization method used (standard or non-standard method of sterilization). The draft guideline EMA/CHMP/CVMP/QWP/BWP/850374/2015 – "Guideline on the sterilization of the medicinal product, active substance, excipient and primary container" should be also considered as the sterilising processing consists sometimes by a combination of non-standard sterilization process (sterile filtration) and aseptic processing. **Proposed change:** The state of process validation of aseptic processing and lyophilisation should be briefly described (if applicable), taking into consideration that these are non-standard processes. Taking into account EudraLex Vol. 4, Annex 13, the validation of sterilising processes should be of the same standard as for product authorised for marketing depending on the sterilization method used (standard or non-standard). The dossier should particularly include information directly relating to the product safety, i.e. on bioburden and media fill runs.	There is no need to distinguish between standard and non-standard processes. The proposal does not increase the clarity of the text.
476 - 478	1	**Comment:** ACRO recommends that consideration should also be given to the GMP status for the grade of	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		excipient used in the IMP manufacture. **Proposed change:** Revise the statement to read: "References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. For excipients not covered by any of the aforementioned standards, an in-house specification should be provided. Consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture."	The added value of including the GMP status is unclear.
483	1	**Comment:** ACRO concurs that validation data on the analytical procedures applied to the excipients are not required in a clinical trial application, and welcomes this recognition.	The comment is noted.
485	1	**Comment:** ACRO recommends that consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture. **Proposed change:** Revise the statement to read: "For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified. Consideration should also be given to the GMP status for the grade of excipient used in the IMP manufacture."	Not accepted. The added value of including the GMP status is unclear.
503-504	4	**Comment:** Need to ensure consistency in expectations between P.5.1 and S.4.1 for the following sentence:	Accepted. Consistency between section P.5.1 and S.4.1. has been ensured.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"The same principles as described for setting the active substance specification should be applied to the medicinal product." **Proposed change:** None specified. The BWP is requested to ensure that expectations for specifications are consistent between active substance and drug product.	
511-514	5	**Comment:** 'Record' or 'report results' should be acceptable in Phase I and Phase II trials for non-critical parameters when data is limited. It is important that sections S.4.1 and P.5.1 are aligned (see above comments for lines 270-271). **Proposed change:** We suggest revising as follows: Since the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, their nature is inherently preliminary. **In such cases (e.g., dissolution for immediate release oral dosage forms), a limit of 'record' or 'report results' is acceptable for Phase I and Phase II trials. The acceptance criteria** ~~They~~ may need to be reviewed and adjusted during further development.	Not accepted. The proposed addition is not applicable for biological IMPs.
518	4	**Comment:** Typographical – insert 'Phase' in the subsection title: 'Additional information for III clinical trials'	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "Additional information for **Phase** III clinical trials"	
539 - 540	1	**Comment:** ACRO recommends that any manufacturing process differences between batches should also be identified. **Proposed change:** Revise the statement to read: "The manufacturing process used for each batch and any differences in these processes should be identified."	Not accepted. Including this type of information in the batch analysis section would be confusing. Furthermore, material from significantly different processes should not be included in the same clinical trial.
558-559	4	**Comment:** The new requirement written into this guideline in P7 to state whether a medical device used bears a CE mark adds additional burden to sponsors in an area which is already increasingly complex with differing national competent authority interpretation around what elements require CE marking and at which stage of clinical development. By specifying that it should be stated as to what bears a CE mark it is likely that this will be interpreted that additional descriptions and justifications will become expected in this part of the IMPD dossier. Allowing for current and future text in the specific legislation the text below is proposed. **Proposed change:** Propose to remove the proposed text "~~If a medical device is to be used, it should be stated whether it bears a CE mark.~~" And replace with "**Where appropriate it should be stated that the**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		device is either 'CE' marked as a medical device or complies with the relevant essential requirements of medical devices as far as safety and performance related device features are concerned. An integral device component of a drug-device combination product, as defined in the MDD, is exempt from CE-marking."	
560-561	2	**Comment:** It is not clear for the possible interactions between parenterals and container closure system, what is the extend of information that should be included in the quality documentation of IMPD in relation with phase I and phase II, III. If a tabulated protocol of the studies will be satisfactory for the phase I, and then later for phase II and III providing the tabulated results would fulfil the requirements, these details should be stated within this paragraph (P.7. - Container closure system).	Not accepted. The level of detail will depend on the situation so it is not possible to be more specific.
571-572	4	**Comment:** Typically 'in use' stability data are presented in P.2.3 or P.2.6 and are complete historical data. P.8 should focus on the drug product stability and shelf-life when under control of the Sponsor to support the label storage conditions. The additional sentence allows the flexibility to provide in-use data in P.2. **Proposed change:** "In-use stability data should be presented for preparations intended for use after	Not accepted. The in-use stability data should be provided in P.8. This is in line with the CTD structure as per the Notice to Applicants.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reconstitution, dilution, mixing or for multidose presentations. **A cross-reference to in-use stability information provided in Section P.2 may be sufficient."**	
571-572	2	**Comment:** It is not clear what is the extend of information requested for in-use stability study in relation with phase I and II, III. Would a protocol be enough for Phase I, II and then later the results to be submitted for Phase III, then these details should be added in the present paragraph.	Not accepted. Representative stability data are expected also for phase I and II. A protocol would not be sufficient.
572-573	5	**Comment:** The section on in-use stability data in this guideline should be aligned with the guideline EMA/CHMP/QWP/834816/2015 (draft 11 April 2016), which excludes oral presentations. **Proposed change:** We would suggest revising as follows: These studies are not required if the preparation is to be used immediately after opening or reconstitution**, or for multi-dose containers with oral solid dosage forms.**	Not accepted. The proposed addition is more relevant for chemical IMPs, but would very rarely apply for a biological IMP.
604-609 and 610-615	4	**Comment:** Reference is provided to EMA guideline EMA/CHMP/QWP/834816/2015 which is generally not in scope of IMPs containing biological/biotechnology derived substances. Please clarify which sections of guideline EMA/CHMP/QWP/834816/2015 are to be considered in the scope of IMPs containing	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		biological/biotechnology derived substances. From the information provided it is not clear whether an authorized comparator product which is only repacked (i.e. secondary packaging) without changing the primary packaging material falls under section 3 or section 4. If it falls under section 4, it is not clear what exactly is required for a modified authorized biological comparator product where the only modification is the change of the secondary packaging and the label. Lines 610 – 615 for modified biological test and comparator products where the IMPD would follow the guidance herein rather than small molecule guidance. Proposed change: Lines 604 – 609 for non-modified, authorised biological test and comparator products where changes to secondary packaging and labelling may occur; add: **In the case when repackaging (secondary) only is performed, without changing the primary packaging the following information should be included in the simplified IMPD in addition to the requirements listed in section 3 of EMA/CHMP/QWP/834816/2015:** • **Information that will satisfy the purpose of the requirement to ensure that the investigational drug will have the proper identity, strength, quality and purity (e.g. cross-reference to the SmPC for the EU marketed product)**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• **Details on the site of repackaging/relabelling operations.** **Lines 610-615** for modified, authorised biological test and comparator products: Information on the modified authorised test/comparator product provided in the IMPD should meet the requirements as outlined in **this guideline** ~~Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).~~ **Sections not impacted by the modification may cross-refer to the approved section."**	
622 - 650	1	**Comment:** Additionally, there is a specific need to include guidance on the commonly encountered situation where there is a change in material of the container used for administration of the IMP, e.g. in the case of a concentrate for solution for infusion that is diluted prior to infusion and administered via infusion from a saline bag, does the change to an infusion bag manufactured from a different type of plastic (e.g., polyolefin instead of PVC) warrant a substantial modification? **Proposed change:** Clarify whether a change of material for an infusion bag would constitute a substantial modification.	Not accepted. This is considered too much detail. It is not feasible to cover all possible scenarios in this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
624-626	4	**Comment:** The text as currently proposed is very specific on a point of Good Manufacturing Practice. This level of specificity is more appropriate to the relevant GMP guidelines and not a regulatory guideline document such as this. Otherwise there is the potential for discrepancies to arise over time between regulatory and GMP guidance. On this basis the proposal is to remove some of the specificity from the current proposed text as described below. **Proposed change:** In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP. ~~at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions.~~	Not accepted. The requested information should be available but does not need to be included in the IMPD.
640-641	4	**Comment:** This bullet point seems to be redundant with a shelf-life extension that would go beyond the duration outlined in the agreed stability protocol (line 638) **Proposed change:** Please delete bullet point: ~~"Any extension of the shelf-life outside the agreed protocol or without prior commitment (see sections S.7 and P.8)."~~	Partly accepted. The first bullet point has been deleted. The second one is maintained as it covers not only a change in the duration but also other changes to the protocol.
644-645	4	**Comment:** • *'each additional extension of the shelf-life is not more than double <u>or</u> more than twelve*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		months longer than the approved shelf-life' The above is contradictory to: • *'shelf-life extensions that goes beyond the duration outlined in the agreed stability protocol'* Furthermore, 'or' is considered to be incorrect as it is understood that both conditions are required for shelf-life extrapolation. **Proposed change:** Revise bullet point in lines 644-645 to read: "each additional extension of the shelf-life is not more than double ~~or~~ **and is not** more than twelve months longer than **available real time stability data'** ~~the approved shelf-life~~"	
Missing issue	1	**Comment:** For IMPs that are proposed biosimilars, it would be helpful if the document included guidance on where the biosimilarity exercise information should be provided within the IMPD. In the absence of current guidance, the experience of ACRO member companies is that a number of sponsors have included a Regional section at the end of the IMPD, after the appendices. This has been accepted by national competent authorities, but clear guidance from the EMA would be welcomed by sponsors and CROs. **Proposed change:** Include guidance on where the biosimilarity exercise information should be provided	Not accepted. Biosimilarity is not assessed at the stage of a clinical trial application.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		within the IMPD.	