EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 May 2016
EMA/CHMP/BWP/337128/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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)

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

Stakeholder no.	Name of organisation or individual
1	Active Pharmaceutical Ingredients Committee / European Chemical Industry Council (APIC)
2	BioPhorum Operations Group (BPOG)
3	Bio-Technology General (Israel) Ltd (BTG)
4	College ter Beoordeling van Geneesmiddelen (CBG-MEB)
5	Dutch Association of Research Quality Assurance (DARQA)
6	European Biopharmaceuticals Enterprises (EBE)
7	European Generic Medicines Association (EGA)
8	International Society for Pharmaceutical Engineering (ISPE)
9	Laboratoire français du Fractionnement et des Biotechnologies (LFB)
10	Parenteral Drug Association (PDA)
11	Paul-Ehrlich-Institut (PEI)
12	Sanofi Pasteur
13	SciencePharma (Poland)
14	Prof C. Demetzos and N. Pippa, National and Kapodistrian University of Athens (UOA)
15	P. Zorzi

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
2	The BPOG team believe the draft guideline is generally well thought through and well written. It is encouraging to see potential for flexibility in using traditional or enhance approaches and combinations of these for process validation.	N/A
2	There is a general concern over the use of non-ICH terms, e.g. Process indicator is not defined nor is it an ICH term – this needs consideration – what is it/are they, how do they relate to validation especially in the context of criticality? To allow for clarity in global development activities the document would benefit from increased harmonization of terms with ICH Q9 concepts on quality risk management as well as guidance from other regions such as the FDA process validation guidance. For example the definition of "Ongoing process verification" could be aligned to the FDA definition of "Continued process verification". The Company thinks that this draft guideline would benefit from additional clarification on the terms "continuous process verification "and "on-going process verification" and their scopes.	"Performance indicator" has been added to the glossary. "Ongoing process verification" has also been added to the glossary. It is the term used in EU nomenclature to avoid confusion with continuous process verification. The guideline indicates that ongoing process verification is also known as "continued process verification" which is the term used in the FDA Guidance for Industry on Process Validation Continuous process verification is defined in ICH Q8 and a reference is made in this guideline.
2	The BPOG team thinks that this draft guideline would benefit from additional sections providing clarification on the following subject areas: 1. Clarifying expectations on the demonstration of the acceptability of the use of small scale modelling in the context of process validation. 2. Clarifying the expectations for continuous process	1) Guidance related to the use of small-scale models in the context of process validation is provided in sections 4.2 and 5 of the guideline. 2) This is a case-by-case situation hence no further detailed guidance can be provided. In addition the future ICH Q12 guideline on Lifecycle Management should address this topic.

Stakeholder no.	General comment	Outcome (if applicable)
	improvements and potential pathways for the associated process validation activities. What would be the regulatory requirements for a manufacturer to implement a well-studied process improvement solution for a commercial process, if there exist sound process understanding, solid data from representative scale down models, and an established “on-going process verification” or “continued process verification” system. 3. Clarifying the expectations for the appropriate process validation of additional manufacturing trains in the same facility.	3) Wording has been added to clarify expectations.
2	It would be helpful if more guidance could be provided on continuous process verification in terms of requirements (types of data, statistical approaches etc.).	Additional guidance on continuous process verification has been included but it should be note that this is a case-by-case situation with very limited experience at present.
2	The companies think it would be helpful to keep the document on “what”, instead of “how”.	Agreed.
2	The companies felt that the level of detail varies through the document. For example, the evaluation section contains examples and delves deeper than verification section. The team think the verification section should be the key for this document. If this is the case, it would be helpful if the level of detail provided could be more consistent.	Process verification builds on process evaluation which is key to support process validation for biotechnology-derived active substances.
6	EBE welcomes very much the opportunity to provide feedback to the BWP on the draft document entitled “Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission “,	N/A

Stakeholder no.	General comment	Outcome (if applicable)
	EMA/CHMP/BWP/187338/2014. The draft guideline is well written and has a good balance between concepts and specific topics. It is also welcomed that examples are included for clarification of scope. We have several general comments which are summarised below:	
6	EBE recognizes that this BWP draft guideline is to a large extent harmonised with the US-FDA guidance on process validation in terms of documentation requirements, however regarding terminology, we would like to suggest that the nomenclature in the BWP guideline should also be aligned with other major process validation guidelines, if possible, e.g. regarding “continued” vs “ongoing” process verification, and process verification vs. process qualification. It would also be worthwhile to clearly explain the differences between process characterisation and process evaluation.	The structure of the guideline has been reorganised to illustrate the different activities in process validation and corresponding terminology: • Process characterisation covers process development and process evaluation; • Process verification can be traditional, continuous and, exceptionally, concurrent (referred to as concurrent validation); • Ongoing process verification. Terminology used in this guideline follows as much as possible existing EU and ICH terminology. Ongoing/continued/continuous process verification: see comment above.
6	We noticed an omission in this document regarding discussion and guidance on concurrent validation studies that we feel would be beneficial to include. In this context, the BWP could consider adding a section on how to enable accelerated programs (e.g. in case of drug shortage, adaptive licensing). It is suggested to request suitable process evaluation	Brief guidance on concurrent validation was included to cover exceptional circumstances such as urgent medical need. Unlike concurrent verification, ongoing process verification is the demonstration that the process remain in a *validated*

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	studies and allow the lack of process verification data in S.2.5 at the time of submission if leveraged by inclusion of an appropriate protocol describing ongoing/continued process verification.	state during the product lifecycle and reference to a protocol in this context is present in the guideline.
6	We suggest using a consistent wording to identify the “commercial scale”; at the moment other terms such as “full scale” or “final manufacturing process” are used in the draft guideline as well.	Commercial scale is used in the guideline.
6	The use of the terms validation, verification and evaluation is sometimes confusing. Care should be taken to ensure that the appropriate wording is used in the appropriate context as verification and evaluation are subsets of validation as outlined in the introduction section.	See above.
6	There needs to be consistency in terms of scope of validation, e.g., different sections give different scope. Some sections suggest that this is only based on criticality and other suggest a wider scope. For example, lines 89-98 would seem to indicate that the scope includes elements that impact CQAs whereas other sections (lines 80-82) indicate other requirements that are not well defined – process indicators? The scope needs to be properly defined and consistently applied across the document.	Both potentially critical and non-critical needs to be addressed but critical needs to be covered in more detail.
6	Inclusion of process indicators is welcome and appropriate, since it is aligned with ICH Q10 as a measure of process performance. Please consider providing a means to identify those process inputs that are of impact to process indicators (process performance) that do not meet the ICH definition of critical process parameters. ICH currently lacks a framework to describe the inputs and outputs that	If the outcome of the studies evaluating the impact of process parameters on CQAs is a consistent product, no similar work is expected on impact of process parameters on process indicators, unless for example there is inconsistent yield at a specific step (in such case the root cause should be investigated).

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	describe the performance aspects of processes. It is not fully clear where to include the process evaluation data in the CTD; we suggest this should normally be S2.5, in justified cases it might also be cross referred to data presented in S2.6. In general we would appreciate corresponding guidance in the document where to describe the development of the control strategy vs. description of the confirmation of the control strategy. In this context it is important to highlight that it is EBE's understanding that there is flexibility with regards to the regulatory binding nature of the information provided in S2.5 (vs. S2.2 and S2.4). Whereas S2.2. and S2.4 are a binding description of the manufacturing process, the information provided in S2.5 should not be regarded as change-relevant but rather as a snapshot of one moment in the lifecycle of the product resulting in the following proposals: • with regards to non-CPPs, we suggest to include a description of those non-CPPs in the process validation section (S2.5) that do have an impact on performance indicators. • Process indicators could be a non-CQA and similar considerations as outlined above for non-CPPs could apply to the description of non-CQAs in S2.5. • S2.5 would then also seem to be suitable to contain a description of the NORs.	Agreed. Control strategy is not in the scope of the guideline and is already addressed in ICH Q11. The importance of the discussion on binding/non-binding nature of the information in the different CTD sections is acknowledged but is an issue beyond this guideline. It will be discussed in the context of ICH Q12.
6	EBE proposes an alignment and reflection in the guideline on the process parameter and performance indicator terminology and would like to make reference in this context to the industry presentations	Agreed. The term "performance indicator" is used in the guideline and a definition referring to ICH Q10 has been included.

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	given at the EMA BWP expert workshop on process validation in April 2013 – please see link: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/04/WC500142338.pdf ; extract from slides 2&3: ***Process Parameter****: Defines the input variable that can be directly controlled in the process;* ***Performance indicator****: Defines calculated or measured process output.* ***Examples:*** • ***Inputs*** - ***Process Parameters*** ▪ *Temperature, Starting Cell Density, etc* ▪ *Raw material attributes* • ***Outputs*** - ***Critical Quality Attributes*** ▪ *Glycosylation, C-terminal processing, etc* - ***Performance Indicators*** ▪ *Seed train parameters – final cell density, etc* ▪ *Cell concentration and/or Viable cell count at harvest* ▪ *Product concentration/ titer at harvest* ▪ *performance indicator from the harvest but process parameter in the load for the recovery step*	
6	There is very little detail provided on continuous process verification in terms of requirements (types of data, statistical approaches, etc.); more guidance would be useful.	See above

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6	We also propose to introduce a paragraph about alternative verification approaches, e.g.: *"Matrix/family approaches to process validation, where multiple similar products, presentations or equipment are grouped together within one validation exercise to reduce the overall testing requirements, may be acceptable if justified by the applicant."*	Presentation is a finished product issue and equipment is GMP-related information, hence not relevant for this guideline. In general it is considered that the current text opens for use of prior knowledge/ platform data cover the issue with matrix/ family approaches. Its applicability depends on the justification that the data is representative for the proposed product and this will be considered case by case.
7	We welcome and appreciate the unique opportunity to share our opinion and comments on the draft 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). We would like to promote the composition of the final version of the document. The draft contains some helpful and concrete elements, however other, especially more general aspects would benefit from further consideration.	N/A
7	The Guideline on process validation for finished products - information and data to be provided in regulatory submissions as published in 2014 (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1) and the FDA PV guideline, 2011 describes a lifecycle approach for PV in the introduction section. For consistency reasons, it would be helpful to implement this guidance as well in the introduction section of this guideline. Please see our wording proposal in the specific comment below.	Agreed.
7	The draft should not overrule the scope for GMPs as defined in ICH	GMP considerations are outside the scope of this guideline.

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	Q7 and Q10. More specifically we propose to clearly separate small scale development studies in the lab or pilot scale where GMPs do not apply from the manufacturing of material for human use where GMP applies.	
7	We propose to clearly specify the information gained at the 'Process Evaluation' stage and where this information should be placed in the CTD (e.g. we strongly feel that small scale data should not be put in CTD S2.5).	General references to CTD sections have been included in the guideline but it should be noted that binding/non-binding nature of the information in the different CTD sections is an issue beyond this guideline. It will be discussed in the context of ICH Q12.
7	Please check the guideline for consistency with regard to the different validation phases and with the descriptions in the ICH guidelines. E.g. chapter 4 (process development) and chapter 5.1 (process evaluation), both describe the development activities (see ICH M4, Q7, 10, 11)	See above.
7	We feel that process development and process evaluation are closely linked to each other. Both are considered to be prerequisites for entering the process verification stage. We therefore propose to combine those two stages under one term and converge the terminology of the EMA with the FDA guidelines as follows: Process design (stage 1) = process development + process evaluation Process qualification (stage 2) = process verification	Even if we do not agree to converge exactly with US nomenclature, the structure has changed in line with the proposal. See above.
7	The nomenclature should be consistent through the guideline. The	Agreed.

Stakeholder no.	General comment	Outcome (if applicable)
	terms “material attributes, process parameters”, “quality attributes, process indicators” (line 80/81) “process conditions” and “performance parameters/indicators” (e.g. line 254/255) and “process parameters and performance indicators” (e.g. line 271) are used in the text. We propose to use the terms process parameters and attributes (e.g. material) for inputs and process performance indicators and attributes (e.g. quality) for outputs.	
7	The concept of concurrent process validation is missing. However, this is sometimes a very useful option, especially in the post approval setting or for reprocessing cases. Therefore we recommend to include the option for concurrent process validation.	Agreed.
7	We would welcome if the guideline can better describe where to put information in the CTD. More specifically it would be helpful to provide guidance, where contents as process evaluation, control strategy (according to ICHQ11) and shipping and transport validation can be placed in the CTD.	See above. Control strategy is not in the scope of the guideline and is already addressed in ICH Q11. There is a brief reference to shipping and transportation of intermediates and active substance but it should be noted that GMP considerations are outside the scope of this guideline.
4	The main line of reasoning of the Guideline, and the distinction between process evaluation and process verification (including associated descriptions, and requirements related to small scale models and the performance of verification studies in accordance with NORs) is valuable and should be retained in principle (acknowledging that further fine tuning of text, based on comments	Agreed.

Stakeholder no.	General comment	Outcome (if applicable)
	from all stakeholders, is acceptable).	
10	PDA recommends terminology and definitions throughout this guideline be harmonized with other regulatory authorities and include the concepts of lifecycle approach to process validation as per ICH Q8, Q9 and Q10. The use of common language can improve understanding across cultural boundaries and streamline the submission process for both applicants and reviewers. For example the use of the term “process evaluation” may create confusion since process evaluation is typically performed for process changes and on-going monitoring. Perhaps calling it “process characterization and validation studies” may be helpful because it aligns with Annex 15 and would differentiate from full-scale process verification. It is understood that process characterization and validation studies are performed prior to process verification. See also comments to lines 50-57.	See above.
14	Thermal Analysis is considered as one of the most popular techniques in material sciences and engineering. Thermal Analysis is a highly sensitive method to study the thermotropic properties of many different macromolecules (i.e. proteins, lipids, etc). This gamut of techniques has been applied to the pharmaceutical field with studies of excipients, biomaterials, nanomaterials and active pharmaceutical ingredients. Applications of this technique to biotechnological products include the measurement of their thermodynamic parameters and a detailed characterization of thermotropic and phase transition behaviour. Advanced technologies connect physicochemical characteristics (polymorphism, fluidity, surface charge etc.) with the	The issue raised is outside the scope of this guideline.

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	alteration of pharmacokinetics, biodistribution profile of drugs and thus reduction of the side effects. As formulations become more and more complex and characterizing them becomes more difficult, manufacturers have done an excellent work in keeping pace with more precise and sensitive yet more durable instruments. Thermal analysis casts light in a total new scientific perspective by facing drugs as biomaterials and not as plain materials. In the pharmaceutical sciences, only a handful of the techniques are commonly employed but the information gained and phenomena, like aggregation, that can be explored are countless.	
15	This is not a line-by-line comment on the above guideline, but is more a general reflection on Validation concepts, since these concepts have already been addressed in several guidelines, but in an inconsistent manner. The following documents have to be considered: - Three ICH guidelines - Two on Process development: Q8R2 (DP), and Q11 (DS) - One ICH GMP for API: Q7 - Two EU guidelines -One on GMP : Annex 15 (draft) -One on Process validation for DP (NCE and Biotech) -and the one on Process validation for DS biotech, purpose of the present consultation - One FDA guidance on Process validation (2011) <u>1- Inconsistencies already in place between these documents</u> The first comment is on the concept of « process verification » for	See above. The structure has been changed in the updated guideline: the evaluation part is moved together with process development to form process characterisation and large scale verification is handled separately. This is more consistent with the guideline on process validation of finished product where pharmaceutical development and validation is split in different sections. As described in ICH Q11 process characterisation is a very important contributor to the overall process validation and both evaluation and verification studies needs to be performed to assure a proper validation of the process.

Stakeholder no.	General comment	Outcome (if applicable)
	which 3 divergent terminologies are used: « Continuous process verification »: ICH and EU « Continued process verification »: FDA « On-going process verification »: EU The only terminology used in ICH guidelines is « continuous process verification ». The EU has adopted this terminology in its various guidelines, but has also introduced a second concept with « on-going process verification » It is also interesting to mention the discrepancy introduced by FDA compared to ICH, since they used « continued » instead of « continuous ». Moreover the only document to make a link between « on-going » (used in EU) and « continued » (used in the US) is in the EU annex 15 (in the glossary). So this lead to raise the following questions: -What will be the data to be provided -In an EU dossier for i) Continuous… and for ii) On-going/Continued, -In an US dossier under the single headline « Continued… -Does this mean that regarding Process validation, the principles and practices will be different for a given company, when applying in EU and in the US ? Are the information to be included as part of a regulatory submission going to be different? <u>2-Even more inconsistencies are now introduced by the new EU guideline Process validation for DS biotech, particularly regarding the corresponding EU guideline for DP</u>	

Stakeholder no.	General comment	Outcome (if applicable)
	In the DS Biotech guideline, Process validation is defined as 2 sequential steps 1st) Process evaluation and 2^{d}) process verification, which is not the case for the EU guideline for DP -Does this imply that for a given product/dossier, a company will have to elaborate two different validation strategies, one for DS and one for DP? -As well as two different information to be in a regulatory submission for validation? At the time of starting the drafting of ICH Q12/Changes in life cycle management, it will be of utmost importance to harmonize terminologies (and concepts?) on Validation.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
32	6	**Comment:** "biotechnology-derived proteins" should read "biotech-derived products" to be consistent with the scope (section2 – lines 65-66) mentioning recombinant proteins, polypeptides, etc. **Proposed change:** The guideline covers process validation of biotechnology derived ~~proteins~~ **products…..**	"biotechnology-derived proteins" was replaced with "biotechnology-derived active substances". In section 2. Scope: - "recombinant" was added to "polypeptides"; - "as defined in ICH Q6B" was removed; - "blood products" was replaced by "plasma-derived products".
32	7	**Comment:** Wording should be consistent throughout the whole document, e.g. "biotechnology derived molecules used as active substance or intermediate". The denomination "molecules" also contains not just proteins but plasmid DNA as active substance that are produced by fermentations. **Proposed change:** "The guideline covers process validation of biotechnology-derived **molecules** ~~proteins~~ used as active substance **or intermediate** in the manufacture of medicinal products."	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
32	10	**Comment:** The opening sentence states that the guideline covers “biotechnology derived proteins” but later in the scope section (lines 65 and 66), it states that polypeptides are covered by the guidance. **Proposed change:** The guideline covers process validation of biotechnology-derived proteins **and polypeptides**…	See above.
34	1	**Comment:** It should be clearly distinguished between the requirements for submission of a marketing authorisation application and variation procedures, especially with respect to the extent of process evaluation studies. In case of variation the applicant identifies the requirements for extent of verification studies and evaluation studies according to the potential impact of the change to quality.	Text was added to capture this point.
34-35	1	**Comment:** No definition of traditional or enhanced approach is included in these draft guidelines, recommend including either a definition in the glossary, or add a cross reference.	A reference to the QWP guideline on process validation where these terms are defined is included.
34-35	2	**Comment:** No definition of traditional or enhanced approach is included in these draft guidelines. **Proposed Change:** Including either a definition in the glossary, or add a cross reference.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
35	6	**Comment:** The guidance includes reference to enhanced and traditional approaches but these terms are not explained in the glossary of terms **Proposed change:** Add a definition of traditional and enhanced validation approaches to the definitions section (or cross refer to ICH Q11 where these terms are defined).	See above.
35	8	**Comment:** Enhanced development and enhanced validation are used very closely and could cause confusion. Particularly as enhanced validation may not have any relationship with enhanced development and enhanced validation is not referred later in the text. **Proposed change:** Recommend using alternate approaches for validation (as used in line 163) when referring to non-traditional validation approaches.	The issue has been clarified as follows: process characterisation can be based on traditional or enhanced approaches, verification can be either traditional or by Continuous process verification.
35	8	**Comment:** Need to clarify “enhanced validation**”**. This could be done in the “Definitions” section or a new section (see below). **Proposed change:** Add definition of “enhanced validation”. It is not very clear whether “enhanced validation” approaches include traditional x runs or x runs prospective and Continuous Process Verification or prospective x runs and future x On-going Process verification? More explicit examples in a new section (rather than in	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the “Definitions” section and embedded in multiple sections) would be an alternative that would help greatly.	
36-37	10	**Comment**: The statement referencing “enhanced approach to process validation” is unclear or perhaps in error. Is this intended to refer to an “enhanced approach to development?” PDA is not aware of a definition for “enhanced approach to validation” and doesn’t see another section referring to this concept. **Proposed change:** PDA recommends clarification of this statement.	See above.
41-43	10	**Comment:** Align guideline with the wording used on the EMA guideline on PV for finished products (EMA/CHMP/CVMP /QWP/BWP/ 70278/2012-Rev 1-Feb 2014). **Proposed change:** Add the following text per EMA PV guide: “Process validation should not be viewed as a one-time event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.”	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
44	6	**Comment:** A Process should always be considered “validated” before put on the market; only the amount of evaluation vs. verification vs. ongoing verification should vary to make this conclusion **Proposed change:** “Normally” to be deleted.	Not agreed. The word “normally” is kept to take into account exceptional cases such as concurrent validation.
45	6	**Comment:** replace “if relevant” **Proposed change:** use “as appropriate”	Agreed.
45-47	7	**Comment:** The Guideline on process validation for finished products - information and data to be provided in regulatory submissions as published in 2014 (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1) and the FDA PV guideline, 2011 describe a lifecycle approach for PV in the introduction section. For consistency reasons, it would be helpful to implement this guidance also in the introduction section of this guideline. **Proposed change:** “… continue through the lifecycle of the product and its process. PV should not be viewed as an on-off event. PV incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production. This document …”.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47	6	**Comment:** Improve clarity **Proposed change:** delete “and its process”.	Agreed.
47-50	6	**Comment:** We suggest a consolidation of the last two sentences for clarification. **Proposed change:** “This document addresses the information, which normally includes process evaluation and verification studies, expected to be presented in a regulatory submission to demonstrate that the manufacturing process described in the CTD section S.2.2 consistently performs as intended.”	Agreed.
50	6	**Comment:** The use of terminology for evaluation, verification and validation exists throughout the document. The distinction between them is not clearly stated until section 5. It should be clearly stated at the beginning so that the reader has a better understanding during review. **Proposed change:** Propose to change line 50 to read, “Process validation ~~This~~ information normally includes process evaluation and verification studies.	Agreed.
51	2	**Comment:** Process Evaluation is new terminology and seems analogous to Process Design in Stage 1. **Proposed Change:** Review Process Design Stage 1 guidance from the FDA and identify level of analogy in this guidance.	Not agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
50-57 and 102-104; 216	10	**Comment:** The terms *"Process Evaluation"* and *"Process Verification"* are interpreted differently by different health authorities and different guidances and so don't clearly differentiate in which CTD section the information should be submitted S.2.5 or S.2.6. **Proposed Change**: To avoid confusion in the industry, PDA recommends EMA harmonize terminology with other regulatory bodies. In addition, PDA recommends that EMA consider Process "Characterization" instead of or in addition to "Evaluation". Characterization encompasses many types of studies (e.g. designed experiments and robustness studies as described in ICH Q8). And consider Process "Validation" instead of "Verification" for consistency with draft Annex 15 terminology. (Please note that section 6.2.3 of this draft uses "validation" terminology in reference with reprocessing.) Other lines in this draft where PDA recommends changing the term "verification" include 102-104 and 216. As a tool to help clarify its recommendations, PDA submits the following table for placement of the different types of information into the corresponding CTD sections.	Comment noted. A figure has been added to the introduction section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><th>Submission Content</th><th>Recommended CTD Section Number</th></tr><tr><td></td><td></td></tr><tr><td>On-going process verification (after Approval)</td><td>S.2.5 or S.2.4</td></tr><tr><td></td><td></td></tr><tr><td>Process evaluation + Process qualification = Process validation</td><td>S.2.5</td></tr><tr><td></td><td></td></tr><tr><td>Process development</td><td>S.2.6</td></tr></table>	
51	6	**Comment:** Section 5 refers to commercial scale whereas section 1 refers to full scale - are these terms interchangeable or should they be aligned? **Proposed change:** Add clarity or make the terms consistent.	Agreed. See above.
51-53	13	**Comment:** It is acknowledged that manufacturing process development is normally not considered as part of process validation. Nevertheless, it is recommended clarifying (after lines 51-53 and/or after lines 102-104) that data required for process evaluation may partially be obtained in the course of manufacturing process development activities.	See above. Process development has been included in the scope of the guideline as part of process characterisation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
51-57	4	The descriptions of process evaluation and process verification activities in lines 51-57 are not fully consistent. The process evaluation is aimed at 'a product of the intended quality', whilst the process verification apparently has the more limited goal of 'meeting its predetermined acceptance criteria'. It is suggested that either the difference is further clarified, or that both descriptions should be harmonised.	See above.
54	2	**Comment:** Process Verification seems analogous to Process Performance Qualification in the FDA guidelines. **Proposed Change:** Review PPQ guidance and make a statement about the level of analogy in this guidance.	See above. Process verification is equivalent to PPQ but is the preferred term for an EU guidance.
58-61	7	**Comment:** It is self-evident that the commercial part of the product lifecycle needs to be performed in compliance with EU GMP. Highlighting the GMP requirement in this line only is unnecessary and in the worst case may lead to misunderstandings. **Proposed change:** Please delete last sentence: "… product lifecycle. ~~These activities have to be performed in compliance with EU Good Manufacturing Practices (GMP).~~"	Agreed.
68-69	5	**Comment:** Could some more guidance on applicability be given within this document?	N/A

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
77-79	2	**Comment:** These two sentences are inconsistent specifically with respect to claim that process development is not part of process validation. ICH Q11 states (emphasis added): "Process validation can include the collection and evaluation of data, **from the process design stage throughout production**, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance." **Proposed change:** Recommend deletion of text before comma: "~~Although not considered as part of process validation,~~ **P**rocess development comprises an essential role in defining the criteria and conditions to be addressed in process validation studies. For further information, please refer to ICH Q11 guideline."	Process development has been included in the scope of the guideline as part of process characterisation.
80-81	6	**Comment:** As stated under general comments, please provide definitions for a "process parameter (input)" and "process indicator" preferably with examples.	The definition of performance indicator (ICH Q10) has been included in the glossary.
80-82	1	**Comment:** Process indicators is a new term in the document, but is not defined in the glossary, recommend adding.	See above.
80-82	2	**Comment:** BPOG believes this text should be clarified to ensure that there is not an implied requirement for excessive additional validation work for minor process steps/units where this might not be scientifically justified. **Proposed change:** "Manufacturing process development should identify which inputs (e.g.	Not agreed. The word "relevant" is covered by the wording above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		material attributes, process parameters) and outputs (e.g. quality attributes, process indicators) for each **relevant** process step/unit operation should be further evaluated during process validation studies."	
80-98	2	**Comment:** The companies felt that different sections give different scope. Some suggest that this is only based on criticality (reference lines 89-98) and others suggest a wider scope yet not well defined (reference line 80-82). **Proposed Change:** The BPOG team think it would be helpful if the scope of the document could be more clearly defined and more consistently applied across the document.	The modification of the guideline has clarified the scope.
80-82 and 99	2	**Comment:** The term "process indicator" is not defined, and it is not clear what it is supposed to represent. **Proposed change:** Include definition of this term in the glossary.	See above.
81	7	**Comment:** The term Process Indicator is used but not defined in the glossary which may lead to different interpretations. **Proposed change:** Define the term "process indicator" as for line 99 and align with the term "Performance indicator" in line 207.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
83	7	**Comment:** "… can help…" seems to be too vague in this context. **Proposed change:** "Documented prior knowledge and risk assessment ~~can help~~ **are valuable tools to** identify and justify the material attributes"	Agreed.
75 - 86	3	**Comment:** Process development may be according to the traditional approach, QbD or combination of the two. **Proposed change:** Suggest relating to the different approaches that may be taken during development in separate paragraphs in the subsections presented.	Agreed, wording added to clarify this.
75 - 86	3	**Comment:** The role of the quality target product profile (QTPP) as a driver in process development is not noted. **Proposed change:** Suggest adding text to tie-in to the QTPP.	Not agreed. Even if the QTPP links to the CQAs and as such sets the basic requirements for the CQAs, it does not have a direct role in process validation.
77	10	**Comment:** When describing process development the draft states "Although not considered as part of process validation..." In PDA's experience, process design is the beginning of the process validation lifecycle, so this statement does not support a lifecycle approach. The statement that "process validation does not end at the time of marketing authorization" (line 46) does support the lifecycle. **Proposed change:** Delete the phrase ~~Although not considered as part of process validation~~ and begin	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sentence "**Process development is an essential foundation for process validation.**"	
89	6	**Comment:** 'Retrospective' process validation should also be described as it might be justified in some instances (ref. is made to ICHQ7 section 12.44 and 12.45). Also, as stated under general comments, a concurrent validation approach might be justified under specific circumstances, e.g. an adaptive licensing project. **Proposed change:** A prospective process validation, as defined in ICH Q7, is expected for biotechnology-derived active substances ***unless otherwise justified (e.g. retrospective or concurrent validation).***	• Description of retrospective validation is not agreed and not in line with revised GMP Annex 15. • Concurrent validation is now mentioned in the guideline.
90-92	11	**Comment:** Consider to shift explanatory sentence from 5. Process Validation (line 90-92) to 1. Introduction (line 45).	The structure of the guideline has been revised.
99	6	**Comment:** The term Process Indicator is used but not defined in the glossary which may lead to different interpretations. **Proposed change:** Define the term "process indicator" and align with the term "Performance indicator" in line 207 (see general comments).	See above.
99	7	**Comment:** The term Process Indicator is used but not defined in the glossary which may lead to different interpretations.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Define the term “process indicator” as for line 81 and align with the term “Performance indicator” in line 207.	
99-101	1	**Comment:** If the expectation is that batches should deliberately be operated outside normal operating ranges, but within proven acceptable range, this could be a challenge to products with a limited number of batches (e.g. where orphan drug status has been assigned).	“Set of controls” replaced with “panel of controls” to clarify wording.
99-101	2	**Comment:** The statement: “The set of controls used in process validation activities (e.g. quality attribute, process indicator, process parameter, controls implicit in the design of the process) are expected to go beyond the routine control system as described in S.2.2 and S.2.4”, raises some questions. Does this mean the monitoring of parameters beyond those indicated in the sections mentioned? Can more clarity be offered here? If there is an expectation that batches should deliberately be operated outside normal operating ranges, but within proven acceptable range (for example to set monitoring up), this could be a challenge to products with a limited number of batches (e.g. where orphan drug status has been assigned).	See above.
99-101	12	**Comment:** We propose to add the sentence below at the end of line 101 ;	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: “In case of process changes, the set of additional controls used in process validation depends on the nature & complexity of change”.	
100-101	5	**Comment:** ‘Are expected to go beyond the routine system as described in S.2.2. and S.2.4.’ is a very vague statement.	Not possible to be more specific since this will be process dependent.
101-105	2	**Comment:** The CTD elements are mentioned here and it would be helpful to have a link to this. **Proposed Change:** Include a link to the CTD format.	Not agreed. General references to CTD sections are included.
102-104	6	**Comment:** The sentence "considering that evaluation and verification activities are often investigated in the same study..." is unclear. For biotech processes, process evaluation aiming at demonstrating that the process steps and the complete process are capable of performing as intended is usually done at small scale while the process verification is, by definition, performed at the commercial scale. It is not clear consequently how these activities are part of the same study. If process evaluation and process verification are done at the same commercial scale, and verifying that the process performs as expected, then it is not clear why it is necessary to create two specific sections: process evaluation and process verification. **Proposed change:** Replace "considering that evaluation and verification activities are often investigated in the same study..." with “**considering that evaluation and verification activities are**	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		normally interlinked" or similar wording.	
105	6	**Comment:** Please see general comment above with regards to the regulatory binding nature of the information provided in S2.5.	Not agreed. See above.
106	2	**Comment:** The companies think it would be beneficial to provide guidance on where to include the Process evaluation data in the CTD.	General references to CTD sections have been included in the guideline.
107-110	2	**Comment:** As above, this text should be clarified to ensure that there is not an implied requirement for excessive additional validation work for minor process steps/units where this might not be scientifically justified. **Proposed change:** "Process evaluation studies should provide evidence that, when operating in accordance with the Description of manufacturing process and process controls (CTD section S.2.2), the complete manufacturing process and each **relevant** step/operating unit have been appropriately designed and controlled to obtain a product of the intended quality."	Proposed text not agreed but other text added to explain the issue. See above.
110-111	10	**Comment:** PDA suggests that "control strategy" be used instead of "control" since a comprehensive control strategy includes BOTH control and monitoring and the word "control" suggests inputs only. Control Strategy is also terminology consistent with ICH.	Agreed. What is meant here includes input and output.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Successful process evaluation should thus demonstrate that the design of the manufacturing process and its control **strategy** are appropriate for commercial manufacturing.	
113-115	2	**Comment:** The term 'control strategy' a familiar one in the industry now. Statements here could acknowledge that the control strategy shows how parameters will be kept within an acceptable range. **Proposed change:** The text could usefully be replaced by (or include) a statement that the control strategy shows how critical parameters will be kept within an acceptable range.	Not agreed. It is important to demonstrate how a conclusion was reached on (non)-criticality.
115	6	**Comment:** Input and outputs not studied further have a rationale for how these are kept within the range to be non-critical. Exact data might not present to be shown – delete "that has been shown" Proposed change: Please change to "…that these are kept within a non-critical range."	"*kept within the range that has been shown to be non-critical*" has been replaced with "*kept within the range that has been shown to have a non-critical impact*".
119-121	1	**Comment:** Some revised text is proposed to clarify this statement: During the process evaluation stage, the proven acceptable ranges should be determined based on the outputs meeting predefined acceptance criteria.	This comment has been addressed.
119-121	2	**Comment:** The statement "These data should demonstrate that when operating within the proposed input ranges, the output meets relevant quality criteria	This comment has been addressed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(i.e. predefined acceptance criteria or internal limits), and thus support the proven acceptable ranges (PAR)." Could be clarified. **Proposed change:** "During the process evaluation stage, the proven acceptable ranges should be determined based on the outputs meeting predefined acceptance criteria."	
120	6	**Comment:** At the time of evaluation, the ranges to be used are only anticipated/preliminary ranges and may only become acceptance criteria or internal limits upon successful completion of the study (i.e. for verification). **Proposed change:** "i.e. ~~predefined~~ **preliminary** acceptance criteria or internal limits"	Not agreed. Preliminary or not, acceptance criteria should to some extent be predefined for evaluation studies.
120	7	**Comment:** In line 120 it states "acceptance criteria or internal limits" for evaluation studies: often the output for each intermediate step is not yet numerically defined at the beginning of the evaluation study, e.g., due to ongoing development of analytical methods, not yet available understanding of the linkage of process steps meaning that process steps can compensate each other's performance. **Proposed change:** "… relevant quality criteria (i.e. ~~predefined acceptance criteria or internal limits~~ **target criteria**), and thus support …"	Not agreed. This term is too vague and may only apply early during development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
120, 221	2	**Comment:** Perhaps "i.e." is not appropriate here. Propose to use "e.g." **Proposed change:** "These data should demonstrate that when operating within the proposed input ranges, the output meets relevant quality criteria (e.g. predefined acceptance criteria or internal limits), and thus support the proven acceptable ranges (PAR)." "Where multiple harvests from one cell culture run are collected, it should be demonstrated that the increasing cell age during the culture run does not have an impact on quality and intra-batch consistency (e.g. derived from initial harvest through to last harvest) and inter-batch (e.g. derived from different fermentation runs / cell culture cycles)."	Not agreed. What is referred to are not examples.
121–123 and 145	6	**Comment:** Historical studies may also be relevant in order to define the control strategy. We suggest that this documentation is given in 3.2.S.2.6. In general, EBE is of the opinion that the topic of "prior/ platform knowledge" would make an excellent topic for a future expert workshop with the BWP. **Proposed change:** In addition to the statement in line 145 it might be worthwhile adding the following sentence after line 123: "*The outcome of the evaluation studies together with e.g. historical studies* ***(platform knowledge)*** *serve as the main basis of defining the control strategy and*	Reference to platform manufacturing/data has been included in the guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		*also in setting the acceptance criteria for the verification studies. Data from **these previous** evaluations should be given in 3.2.S.2.6*".	
121 - 123	3	**Comment:** Control strategy is referred to but it is not clear if this is to the finalised control strategy. **Proposed change:** Add clarification to the text.	The following sentence was added: "*Elements of the control strategy may be optimised following the outcome of the verification studies*".
124-127	1	**Comment:** Another option (e.g. for products with orphan drug status) would be to perform a risk assessment of the process cumulative hold information from at-scale batches. This could include use of platform data where appropriate and could continue to be performed as part of the ongoing process verification program. A risk assessment could also be performed to determine the requirement for spiking studies (e.g. if consistent amounts are added, in process monitoring may suffice).	Not agreed. The current text allows for different options "where appropriate (…)".
124-127	2	**Comment:** The stated approach in the guidance may not be the only way to demonstrate robustness: "Where appropriate, evaluation of selected step(s) operating in worst case and/or abnormal conditions (e.g. cumulative hold time, spiking challenge) could be performed to support or demonstrate the robustness and the capability of the process to deliver product of the intended quality in these conditions."	Not agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Enable situations like the following to be seen as acceptable. Another option (e.g. for products with orphan drug status) would be to perform a risk assessment of the process cumulative hold information from at-scale batches. This could include use of platform data where appropriate and could continue to be performed as part of the ongoing process verification program. A risk assessment could also be performed to determine the requirement for spiking studies (e.g. if consistent amounts are added, in process monitoring may suffice).	
124 and 290	4	**Comment:** The term “abnormal conditions” is unclear. Clarification should be considered, and/or another term may be used, e.g. ‘extreme’, ‘boundary’, non-routine’ or ’non-standard’ conditions, depending on what is exactly intended.	“abnormal” was replaced with “non-standard”.
124	6	**Comment:** “abnormal conditions” may be misunderstood; suggest to replace by “**non-standard**” **Proposed change:** “~~abnormal~~ non-standard conditions”	Agreed. See above.
124	10	**Comment:** PDA recommends that the identification of “worst case” should cover any process variations that can be foreseen. The use of the term “abnormal conditions” suggests it is necessary to test unexpected and unforeseen conditions. PDA recommends that this	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		guideline avoid suggesting that a process be run under abnormal or uncontrolled conditions. In general procedures are in place to determine what should be done with unexpected conditions. **Proposed Change:** Delete “abnormal conditions”	
124	10	**Comment:** Cumulative hold time is not appropriate worst case for biologics. Some readers may take this list of examples to exclude other characteristics, so a list of examples may not be valuable. **Proposed Change:** PDA recommends to delete the examples because worst case should be determined on a case by case basis for each process.	“cumulative hold time” was removed and the example given is impurity spiking challenge.
124-127	2	**Comment:** The stated approach in the guidance may not be the only way to demonstrate robustness: “Where appropriate, evaluation of selected step(s) operating in worst case and/or abnormal conditions (e.g. cumulative hold time, spiking challenge) could be performed to support or demonstrate the robustness and the capability of the process to deliver product of the intended quality in these conditions.” **Proposed change:** Enable situations like the following to be seen as acceptable. Another option (e.g. for products with orphan drug status) would be to perform a risk assessment of the process cumulative hold information from at-scale batches. This could include use of platform data where appropriate and could continue to be performed as	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		part of the ongoing process verification program. A risk assessment could also be performed to determine the requirement for spiking studies (e.g. if consistent amounts are added, in process monitoring may suffice).	
124-128	8	**Comment:** The examples used in this section (particularly "cumulative hold studies") give concern. The event of a cumulative hold would be extremely unlikely. At scale simulation of a cumulative hold is inconsistent with current validation study design and may be impractical for many long biological processes. As scientifically justified physiochemical hold time studies at a representative small scale may provide the required robust data. Similarly abnormal or spiking studies cannot be done at scale due to risk to product and are much better done in representative small-scale studies. **Proposed change:** Text needs to clarify that some of the work could be done as representative small scale. Abnormal conditions would definitely not simulate at scale. Suggest using alternate examples.	See above.
125	6	**Comment:** "Cumulative hold time" is not a good example due to the fact that the applicant seldom has cumulative hold time studies at the time of submission; they are available at a later stage. There is a concern that this might become a standard requirement at the time of MAA submission.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We suggest to delete “cumulative hold time” as example and propose to add another example, eg. “(spiking challenge, **studies beyond PARs**).”.	
125	7	**Comment:** Please clarify that these studies can be performed at small scale. Proposed change: “… could be performed at small scale models to support …”	See above. Most if not all evaluation studies are expected to be performed at small scale, hence no need to specify in the text.
127-128	1	**Comment:** This may not be appropriate to perform this type of study on process verification batches, especially if a very small number of batches are being performed. Additional monitoring is being performed through the process verification batches, hold times should be part of the continuous process verification.	See above.
127-128	2	**Comment:** The statement “In some cases, these activities could be built into process verification studies (e.g. lots produced with intermediates stored in worst case hold conditions)”, may not give an appropriate approach. It may not be appropriate to perform this type of study on process verification batches, especially if a very small number of batches are being performed. Additional monitoring is being performed through the process verification batches, and hold times could/should be part of the continuous process verification. **Proposed change:** Change the text to account for small numbers of batches and the additional	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		monitoring.	
128	6	**Comment:** "(e.g. lots produced with intermediates stored in worst case hold conditions)." Proposed change: Please change to "(e.g. lots produced with intermediates from worst case conditions)"	This example was removed.
130-131	1	**Comment:** There may be difficulties in obtaining different batches of raw materials from manufacturers during process evaluation stages, especially if this work is performed across a short time frame. A recommendation would be to focus on assessments of critical raw materials and parameters during the process evaluation stage, with monitoring of raw materials to form part of ongoing process verification.	The wording of the last paragraph in section 4. Process evaluation regarding raw material variability was revised.
130-131	2	**Comment:** Whilst the team appreciate the importance of understanding the contribution of raw materials to variation in the process, the statement: "During process evaluation, small scale models enable evaluation of input material and parameter variability to an extent that may not be feasible at manufacturing scale", may be true in some cases, but other factors come in to play. For example, there may be difficulties in obtaining different batches of raw materials from manufacturers during process evaluation stages, especially if this work is performed c-across a short time frame.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: A recommendation could be included to focus on assessments of critical raw materials and parameters during the process evaluation stage, with monitoring of raw materials to form part of ongoing process verification, as this may address availability issues and variation introduced by sampling to provide small quantities.	
132	6	**Comment:** Data may not always be generated for each small scale model, but a justification may be made on previous knowledge. **Proposed change:** Consider changing 'demonstrate' to 'justify'.	Agreed.
132-133	5	**Comment:** '...and ultimately be demonstrated, as an appropriate representation of the manufacturing process'. Is this always realistic in this phase?	See above.
133-139	2	**Comment:** Demonstration at the commercial scale seems to be on the same principles as recent FDA communications. **Proposed change:** Refer to recent FDA communications and acknowledge the use of the same principles.	Not endorsed because not relevant.
137	4	**Comment:** The words between brackets (e.g. design space claimed) do not seem to add any clarity and deletion should be considered.	This is considered as a relevant example.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
138-140	6	**Comment:** Using the same input materials as used in small scale is often not practical or possible. **Proposed change:** "…demonstrate that when operating under the same conditions using **representative** ~~the same~~ input materials…"	Agreed.
145-149	2	**Comment:** Clarify what the criteria are that would justify use of data derived from manufacture of another platform molecule in the validation package. **Proposed change:** Provide examples of criteria that would need to be evaluated and/or justified.	Not agreed. It is the applicant's responsibility to propose an approach.
145 - 149	3	**Comment:** In what section of the CTD should prior information or platform data be included? Need alignment with M4Q for content of CTD sections. **Proposed change:** Include reference in the text.	S.2.6 would be the appropriate location. However, this topic is discussed in the context of ICH Q12, so no specific reference is included in the text.
145 - 149	3	**Comment:** Clarification regarding inclusion of data from all batches used for determination of manufacturing ranges. **Proposed change:** Please add clarification in the text if all analytical results from all batches used for determination of manufacturing ranges need be included in 3.2.S.4.4.	Not endorsed as the proposed text is out of scope of the guideline.
145-149	3	**Comment:** In what section of the CTD should prior information or platform data be included? Need alignment with M4Q for content of CTD sections.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Include reference in the text.	
147-149	6	**Comment:** The sentence refers to verification studies performed at commercial scale; it is recommended to move the sentence to the verification section, e.g. line 155.	The sentence was removed. This point is reflected in section 5.1.
153-154	1	**Comment:** Where a limited amount of data is available or if a limited number of process verification batches are being performed, the use of target ranges may be more appropriate. After sufficient data has been obtained, NORs should be defined.	The term “NOR” was removed from the text. “Normal set point” is used instead. Remark: it is up to the applicant to define their approach for setting ranges.
153-154	2	**Comment:** The statement: “Such studies are generally performed in accordance to the expected normal operating ranges (NORs)”, fails to take into account the level of confidence it may be possible to establish in the operating range at this stage in the lifecycle of the product. **Proposed change:** Include a statement to the effect: “Where a limited amount of data is available or if a limited number of process verification batches are being performed, the use of target ranges may be more appropriate. After sufficient data has been obtained, NORs should be defined.”	See above.
155	2	**Comment:** Suggest to replace “,” with “and” in sentence “Process verification data (including process step results, batch analyses)”	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "Process verification data (including process step results and batch analyses)".	
155-162	2	**Comment:** Consider adding in some language about batch size, and what is considered representative of commercial scale. **Proposed change:** Provide examples of criteria that would need to be evaluated and/or justified.	Not agreed. This will need to be considered on a case by case basis and the choice/ justification is up to the applicant.
155-159	6	**Comment:** The initial intention of this section appears to request results of controls performed during process verification; this should link to section "6. Points to consider in process validation" to clarify the type of information requested. **Proposed change:** "… process description **(cf. section 6 for details)**. Failure to present **verification** ~~validation~~ data on consecutive batches…"	Agreed.
155-162	11	**Comment:** It should explicitly be indicated that the number of batches for which data is presented should be a minimum of three. **Proposed change:** "Process verification data (including process step results, batch analyses) should ~~normally~~ be completed and presented in the regulatory submission on an appropriate number of **at least three** consecutive batches produced with the commercial process and scale, taking into account the batch definition as detailed in the process description."	Not agreed. Reference to the three batches is related to a traditional approach and is covered in the GMP Annex 15. This guideline also addresses enhanced approach. It is up to the applicant to justify the number of batches.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Alternatively, the following option could be used: The number of batches to be presented **is normally three but** depends on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; (3) the amount of experimental data and/or process knowledge available on the process; and (4) the frequency and cause(s) of batch failure.	
155 - 162	3	**Comment:** The discussion of process verification data does not include if and how the robustness of the process is to be described. **Proposed change:** Add explanation in the text.	Not agreed. Robustness is primarily assessed during process characterisation.
156	11	**Comment:** Consider to include explicit examples of situations where number of validation batches for verification study could be reduced using a matrixing approach.	Not agreed. It is not possible to spell this out since it will be a case by case decision and acceptance will depend on the justification of the applicant.
158-159	11	**Comment:** Consider to amendment of the request to justify deviation from the routine/standard approach to produce validation batches in a consecutive manner. Proposed change: “Failure to present validation data on consecutive batches should be appropriately justified including a rational how production of validation batches is scheduled in a pre-defined manner.”	Not agreed. This is a GMP-related matter which is outside the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
163	2	**Comment:** The text says 'ongoing process verification'. Is this the same as 'continuous process verification'? **Proposed change:** Use one phrase if these two things are the same, and define both clearly if not.	See above.
163-166	6	**Comment:** This section may be in contradiction to the ICH Q8 definition since continuous process verification is an "alternative to process validation" and verification is only one part of process validation. In other words, strictly speaking, continuous process verification should normally replace both process evaluation and verification. There is no reduction of the number of batches for the overall process validation program as instead all batches ever produced would likely be integrated into the continuous verification. **Proposed change:** If it is not possible to provide examples, we propose to shorten the section to the ICH definition to avoid further confusion.	See above. It should also be noted that continuous process verification is an alternative approach to traditional process verification.
163-166	13	**Comment:** More detailed information and guidelines on both continuous process verification and hybrid approach would be highly helpful. If provisions presented in the "Guideline on process validation for finished products - information and data to be provided in regulatory submissions" are applicable in this case, reference to this guideline should be made.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
164-165		**Comment:** The aspect is missing that process knowledge is gained during the process development phase. **Proposed change:** "The success of such an approach will be highly dependent on the knowledge and understanding gained on the process and product **during process development and process evaluation**, and the …".	Not agreed to add wording. Process evaluation will by default build on process development but we see no need to spell them both out
164-166	2	**Comment:** It is not clear what is intended by monitoring of inputs and outputs in an "uninterrupted manner". **Proposed change:** Please delete or clarify what is meant by "in an uninterrupted manner". Clarification should be consistent with definition of PAT as found in ICH Q8(r2).	"uninterrupted manner" has been deleted.
166	4	**Comment:** The meaning of the final words of this sentence ('in an uninterrupted manner') is unclear. Deletion or clarification should be considered.	See above.
167-168	6	**Comment:** This section should be in line with the information laid down in the recently published FDA/EMA Q&A on design space verification.	Not agreed. The text is in line.
167-169	1	**Comment:** Suggested re-wording: A protocol should be prepared to detail additional monitoring to be performed within the design space so that it is clear as to what is the valid design space and	Not agreed. The proposed wording follows the wording of Q11.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		what should occur in the event of excursions.	
167-169	2	**Comment:** These lines include the statement: "In the case that a design space is claimed, it may be needed to include a protocol on how movement within the design space will be managed post approval to verify that the design space is still valid when run at commercial scale." **Proposed change:** The team believe this statement could be usefully reworded as follows: "A protocol should be prepared to detail additional monitoring to be performed within the design space so that it is clear as to what the valid design space is and what should occur in the event of excursions."	See above.
169	12	**Comment:** We propose to add a paragraph focused on rarely produced products (less than 1 batch /year) and without continuous process verification. The verification could be performed onto 2 steps after definition of the adequate number of validation batches: - 1st step prospective verification based on one industrial batch and on supportive data from pilot batches - 2nd step concurrent verification on the first next industrial batches produced in order to reach the adequate number of validation batches.	Agreed. Concurrent validation is now addressed in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
170	11	**Comment:** Consider to amend section header (see below) in order to use the same title as used in the respective section in the Draft for Annex 15 to the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. **Proposed change:** 5.3. Ongoing process verification **during lifecycle.**	Agreed.
170	12	**Comment:** International manufacturers have to work with guidelines from different areas and countries. As there is already an FDA guideline used as a reference in industry, we propose to replace “Ongoing process verification” by “Continued process verification”.	Not agreed. See above.
170	6	**Comment:** It would be helpful to mention that ongoing process verification is also referred to as “continued process verification” in other regions to avoid misunderstanding. **Proposed change:** “ongoing **(continued)** process verification”	Agreed.
170-175	6	**Comment:** The intention of these protocols should be clear insofar that: - ongoing process verification are mandatory activities as described in GMP, - protocols submitted in a regulatory filing are not intended to substitute any GMP requirements (e.g. revalidation, annual product review…) but to provide a high level plan on how the validation activities will	Agreed. Additional guidance on ongoing process verification was included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		continue through the lifecycle of the product, - submission of such regulatory protocol in the MAA should normally be optional but if assurance needs to be provided that proper validation activities will be performed prior to supply of the product to the market (e.g. in the case where limited number of process verification data are submitted in the initial MAA), the principles of the ongoing verification program should be described in the submission. It would be helpful to further expand on how to enable ongoing process verification in the MAA, linking these recommendations to the protocols mentioned in the points to consider. **Proposed change:** We propose to add the following text after line 175 as follows: “Ongoing process verification should be conducted under a protocol. The submission of an ongoing process verification protocol in the MAA is not required. However in some situations (e.g. in the case where limited number of process verification data are available at the time of submission), inclusion of the summary of such protocol could facilitate the demonstration that proper validation activities will be performed prior to supply of the product to the market.”	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
171-175	1	**Comment:** There needs to be clarification as to whether ongoing process verification is the same as the Annual Product Review. Further clarification of process validation and process verification are required to ensure they are being used consistently throughout the document. Both terms are included in the glossary, but the differences are not clear.	The difference between “process validation” and “process verification” has been clarified. Annual Product Review is not the same as process verification. It is a GMP feature outside the scope of this guideline.
171-175	2	**Comment:** These lines include the statement: “Subsequent to successful process validation activities for regulatory submission, companies should monitor product quality and process performance to ensure that a state of control is maintained throughout the commercial part of the product lifecycle…”. The team feels this statement risks a lack of clarity. In particular, there needs to be clarification as to whether ongoing process verification is the same as the Annual Product Review. **Proposed change:** Further clarification of process validation and process verification are required to ensure they are being used consistently throughout the document. Both terms are included in the glossary, but the differences are not clear.	See above.
171 - 175	3	**Comment:** Not clear how ongoing process verification is described in the CTD. **Proposed change:** Please add reference to the relevant CTD section where this information should be	See above. The guideline states that *“Process verification information should usually be submitted in Section 3.2.S.2.5 of the CTD”*.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		included.	
177 and 269	10	**Comment:** Sections 6.1 to 6.2.2 are very specific to the upstream and downstream portions of a typical cell culture process. The scope of the document is wider than cell culture and protein production. These sections would be more valuable if they were a statement of principles for PV rather than a worked example of how a cell culture process should be validated. **Proposed change:** It should be acknowledged in section 6.1 that not all recombinant protein products under the scope of this guidance will include a only a cell culture step in the upstream process, therefore additional unit operations in the upstream process should be addressed in this section.	Sections 4 and 5 spell out principle issues. Section 6 describes issues affecting most common types of products.
179 and 187	2	**Comment:** As written, the text implies that the WCB is a starting material. This use of the phrase "starting material" is inconsistent with ICH Q7 which defines API starting material as (emphasis added): "An API starting material is a raw material, an intermediate, or an API that is used in the production of an API and that is **incorporated as a significant structural fragment into the structure of the API**." **Proposed change:** [line 179] "Process validation of the upstream process normally includes evaluation and verification that the cell culture steps, from the	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~introduction of the starting material in~~ **initiation of** the manufacturing process (e.g. thaw of the working cell bank (WCB)) up to the collection of the last harvest obtained at/or beyond production level are capable to perform as intended. [line 186] "Process evaluation activities should demonstrate that the cell culture steps, from the ~~introduction of the starting material in~~ **initiation of** the manufacturing process (e.g. thaw of the WCB) up to and/or beyond production level, are capable of consistently delivering inoculates, harvest(s), and ultimately an active substance of appropriate quality.	
182	6	**Comment:** Validation is comprised of evaluation + verification, therefore please remove "evaluation" **Proposed change:** "… the ~~evaluation /~~validation **studies"**	Agreed. "validation" is used.
183-184	7	**Comment:** We propose the following addition for clarity. Proposed change: "…obtained at a later stage of the process and/or on process analytical technology data obtained during cell culture / fermentation steps".	Not agreed. This comment is not in line with what is meant in the guideline.
186-190	9	**Comment:** In order to support the criticality of USP process parameters the prior knowledge and realisation of the DSP process is required. Actually, the CQAs are linked to the drug product. As a consequence USP and DSP evaluation are linked.	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: 188-189: “and ultimately an active substance of appropriate quality **after DSP**”.	
188	7	**Comment:** Typo “Inoculates” **Proposed change:** “…are capable of consistently delivering **inocula** ~~inoculates~~, harvest(s), and ultimately …”	Noted.
190	2	**Comment:** The statement says: the level of detail provided should support the criticality assignment of process parameters. **Proposed Change:** The level of detail provided should be consistent and appropriate to the criticality assessment of each parameter.	Not agreed. The approach to support the assignment of criticality and ranges to non-CPPs should be included in the dossier.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
191-195	14	**Comment:** Proteins are characterized by dynamics and flexibility. There is interplay between the structure and the dynamics of biomaterials (i.e. proteins etc.). Thermal analysis techniques can provide their thermodynamic signature and quantify their biophysical behaviour. **Proposed change :** "*These activities could include evaluation of specific cell traits or indices (e.g. morphological characteristics, growth characteristics (population doubling level), cell number, viability, biochemical markers* ***and their biophysical behaviour****, immunological markers, productivity of the desired product, oxygen or glucose consumption rates, ammonia or lactate production rates), process parameters and operating conditions (e.g. time, temperatures, agitation rates, working volumes, media feed, induction of production).*"	Not endorsed because this comment is outside the scope of this guideline.
199	6	**Comment:** We suggest to replace "microbial purity" with "bioburden" (see ICH Q7). **Proposed change:** "(e.g. yield, maximum generation number or population doubling level, consistency of cell growth, viability, duration and **bioburden** ~~microbial purity~~) should be presented."	Not agreed. In case of prokaryotic systems, bioburden would also include the production system. Since the intention of the test is to verify absence of contamination microbes, microbial purity is kept.
200-205	12	**Comment:** We propose to add the following statement after the end of the first sentence at the beginning of line 203: "These studies should be conducted as early in the development process as possible at small scale.	Raw material variability addressed under 4.2. Process evaluation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It may not be feasible to perform simultaneous assessment study of raw material variability at large scale.	
207	6	**Comment:** The term Performance Indicator is used but not defined in the glossary which may lead to different interpretations. **Proposed change:** Define the term “Performance indicator” and align with the term “Process indicator” (in line 99).	Agreed. See above.
207	6	**Comment:** This section suggests validation against NORs. There should be no requirement to register a change to the NORs if the process continues to run within the PARs. **Proposed change:** See general comment regarding chapter S2.5 and information to be included that should not be change-relevant.	The term “NOR” was removed from the text. “Normal set point” is used instead. Binding/non-binding nature of the information in the different CTD sections is an issue beyond this guideline. It will be discussed in the context of ICH Q12.
207	7	**Comment:** The term Performance Indicator is used but not defined in the glossary which may lead to different interpretations. **Proposed change:** Define the term “process indicator” and align with the term “Process indicator” in line 81 and 99.	See above.
207-210	1	**Comment:** If a small number of commercial scale batches have been performed, initial process verification may be better defined by PARs. NORs should be defined by the time the product is in	The term “NOR” was removed from the text. A definition of PAR was included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		commercial phase.	
207-210	2	**Comment:** The statement "Process verification activities should focus on the confirmation of consistency of performance indicators and quality attributes when operating conditions and process parameters are in accordance to NORs." Does not seem entirely appropriate to the team. **Proposed change:** Take account of the fact that; if a small number of commercial scale batches have been performed, initial process verification may be better defined by PARs. NORs should be defined by the time the product is in commercial phase.	See above.
209	7	**Comment:** As this chapter is only for upstream process we propose to add here "upstream" for clarity. **Proposed change:** "These studies should include all culture steps and cover the complete duration of the **upstream** process, on an appropriate number of consecutive batches."	Agreed.
211	3	**Comment:** General issues related to single use equipment which seem to only relate to the upstream process. **Proposed change:** Suggest relating to the downstream process as well.	Main experience is gathered from upstream processing and therefore it is placed in the upstream section. The principles described apply for downstream as well where appropriate.
211-217	6	**Comment:** We suggest rephrasing this paragraph to align validation (evaluation + verification) terminology and better reflect a risk-based approach (ie.,	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		consumables should be risk-assessed based on their intended use and proximity to the active substance). **Proposed change:** "When single use equipment is used in ~~development~~ **evaluation** studies, consideration should be given to leachables and extractables. Information should be provided on the nature and amount of potential leachables, ~~their impact on the cell culture~~, and the removal of such impurities. Besides data this normally includes a risk assessment **of their potential impact, e.g. on the cell culture**. For **verification** ~~validation~~ full scale equipment has to be used. Various batches of disposable systems should be used **as appropriate** in the manufacturing of verification batches in order to assess their impact on the product quality."	
211 – 217	8	**Comment:** We suggest to link this section to ICH Q11. For validation full-scale equipment has to be used. Guidance as written appears to preclude any small scale data which can be scientifically justified to provide relevant process development data. Similar to qualifying small scale chromatographic resin characterization, lot-to-lot variability should be well represented by small scale studies with various lots. **Proposed change:** While small scale data are relevant for process development, process verification for disposable systems should be done with full scale equipment. Small-scale data with various batches of	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		disposables should be provided and where feasible process verification should also use various batches for process verification studies.	
212	2	**Comment:** Suggest to delete “in development studies” from the sentence to provide flexibility to consider leachables and extractables in other types of studies. **Proposed change:** “When single use equipment is used, ~~in development studies~~ consideration should be given to leachables and extractables.”	Agreed. See above.
212-213	11	**Comment:** Consider whether insertion of ‘in development studies’ in line 212 is necessary and in line with the heading of the section. **Proposed change:** When single use equipment is used, ~~in development studies~~ consideration should be given to leachables and extractables.	Agreed. See above.
212-217	1	**Comment:** Obtaining different batches of consumables during process verification batches may prove challenging for such batches which are typically performed close together. The recommendation would be to include use of consumables in the ongoing process verification.	Agreed. Wording added to capture this issue.
212-217	12	**Comment:** The level of effort associated with leachable/Extractables studies should be proportional to the risk of the equipment in its operating conditions and the impact on the cell culture and purification process. Risk assessments should therefore be	Comment captured by comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		performed prior to leachable/extractables studies in order to define which type of studies is needed.	
214-215	7	**Comment:** Such data not necessarily need to be generated under actual process conditions. E.g. supplier data or data generated under representative model conditions may be suitable. **Proposed change:** "…includes a risk assessment. Data not necessarily need to be generated under actual process conditions. E.g. supplier data or data generated under representative model conditions may be suitable. For validation full scale equipment has to be used …"	Agreed.
215	7	**Comment:** "For validation full scale equipment has to be used." This requirement appears too strict. We believe that representative small scale and predictive model studies may contribute at least for the process evaluation part of the process validation. Proposed change: "For ~~validation~~ process verification studies full scale equipment ~~has to~~ should be used. During process evaluation small scale or predictive model studies are acceptable to assess leachable profiles, leachable removal and the impact of such impurities on cell culture performance".	See above.
215-217	7	**Comment:** Different batches of single use equipment may not always be commercially available for each	Deletion not agreed. Wording added to cover issue with availability.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		piece of equipment at the time of process verification. Information regarding the impact of different batches of single use equipment on product quality is further gained during the commercial part of the product life cycle. **Proposed change:** "… has to be used. ~~Various batches of disposable systems should be used in the manufacturing of verification batches in order to assess their impact on the product quality~~."	
215-216	10	**Comment:** It is unclear in the current text whether **"**Various batches of disposable systems…" is intended to mean various batches of flexible disposable materials making up a disposable system or various batches of biotech active ingredient or intermediate. **Proposed change:** PDA recommends changing as follows: Various batches of disposable **components** should be used…"	Agreed.
215-217	2	**Comment:** In this section on single use equipment, the BPOG team thinks that the text below is potentially confusing and could be interpreted as being unnecessarily definitive. The Company has suggested replacement text to allow for more potential flexibility, where justified. Obtaining different batches of consumables during process verification batches may prove challenging for such batches which are typically performed close together. The recommendation would be to include use of consumables in the ongoing	Covered by rewording.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		process verification. **Proposed change:** "Variability in disposable systems should be included as part of the process evaluation and risk assessment analysis, or provided through continued process verification (or on-going process verification) if not included as part of verification batches."	
220-222	6	**Comment:** We suggest an editorial change to clarify the sentence. **Proposed change:** ….does not have an impact on quality and intra-batch ~~consistency~~ (i.e. derived from initial harvest through to last harvest) and inter-batch (i.e. derived from different fermentation runs / cell culture cycles**) consistency.**	Agreed.
221-222	7	**Comment:** Typo: The term "consistency" is missing **Proposed change:** "…through to last harvest) and inter-batch **consistency** (i.e. derived …"	Agreed.
231	7	**Comment:** Typo **Proposed change:** "…batches based on several ~~fermentations~~ **fermentation** runs/ cell culture cycles …".	Agreed.
231-234	6	**Comment:** We suggest an editorial change to clarify the sentence **Proposed change:** The verification of ~~the~~ **batch** consistency ~~of batches~~ based on several fermentations	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		runs/ cell culture cycles could lead to the necessity of producing a large number of batches spanning a long production period. In such situation, an applicant may propose a protocol to verify ~~the~~ **batch** consistency ~~of these batches~~ through ongoing process verification.	
233	2	**Comment:** This statement could mean that the number of batches required in PPQ could be reduced if ongoing process verification is justified. **Proposed change:** Clarify whether the number of batches in PPQ could be reduced if justifiable through ongoing process verification.	As explained in the guideline: - Section 5: "*Successful demonstration of the suitability of the small scale model could reduce data requirements for process verification (e.g. reduced number of batches)*". - Section 6.3: "*In case the differences between the sites are not major and it can be demonstrated that the previous validation studies are suitable representation of the new site, the ongoing process verification could reduce the amount of process verification data to be submitted*".
243-253	7	**Comment:** For evaluation of the downstream process, especially for the clearance of process related impurities, reference is made to spiking experiments and the establishment of analytical methods. We believe that for some components (e.g. media components) a risk-based approach based on a theoretical evaluation is sufficient. E.g. by calculating the maximal amount of the media components which can be present in the medicinal product, also considering the final dosage administered to the patient. **Proposed change:** Add after line 253: "For some components (e.g. media components), a risk-based approach is acceptable showing that no safety	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		concerns like immunogenicity or toxicity is given in the final dosage form".	
246-248	14	**Comment:** The morphology and the shape, as well as the shape/morphology balance of biomaterials are directly related to their colloidal and biological behaviour. From the pharmaceutical point of view, thermal techniques are used in order to evaluate the physicochemical properties of drugs and their interactions in biological level, as well as their behaviour during the formulation process. **Proposed change:** "*This generally includes establishment of adequate analytical methods* ***(including thermal analysis techniques)*** *required for their detection and an estimation of the concentrating or removing capacity for each unit operation followed by the determination of appropriate acceptance criteria* ***(based on morphological and thermotropic criteria)***."	Not agreed. This comment is outside the scope of this guideline which is what to study and not how.
248-250	7	**Comment:** Add the possibility to validate impurities out of routine testing. **Proposed change:** Add in line 250 "**An appropriate scientific justification (e.g. risk assessments or appropriate number of batches or spiking studies) allows the exclusion of routine testing for impurities"**.	Not agreed because this comment is outside the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
249	6	**Comment:** We propose an editorial change to terminology consistent with the rest of the document **Proposed change:** ~~scale-down~~ **small scale** spiking experiments.	Not agreed. Scale-down is the appropriate term in this specific case.
250-253	1	**Comment:** The recommendation would be to perform a risk assessment around cumulative hold times which could be generated at small scale. Alternatively, ongoing process verification could be used to support cumulative hold times.	Not agreed. The text is not about cumulative hold times but about evaluation of the process.
250-253	2	**Comment:** The team sees the statement: "Evaluation of selected purification step(s) (e.g. steps for which high impurity or viral clearance are claimed) operating in worst case and/or abnormal conditions (e.g. cumulated hold times, spiking challenge) could be performed to document the robustness of the process." As overly prescriptive and would suggest the following. **Proposed change:** The recommendation would be to perform a risk assessment around cumulative hold times which could be generated at small scale. Alternatively, ongoing process verification could be used to support cumulative hold times.	Not agreed. See above.
251-252	6	**Comment:** We propose to change this sentence to **differentiate between** the two scenarios "viral clearance" and "high impurity clearance".	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Evaluation of purification steps for which high impurity clearance are claimed, operating in worst case and/or abnormal conditions (e.g. process hold times, spiking challenge) could be performed to document the robustness of the process. Evaluation of steps where viral clearance are claimed should be performed as described according to ICH Q5A (R1).	
254	6	**Comment:** In order to clarify this sentence, we propose the following changes/ correction of typo. Next to this 'performance parameters/indicators' should be defined. **Proposed change:** Process conditions (e.g. column loading capacity, volumetric flow rate, length **of column** , elution/washing **and/or regenerating** conditions ~~conditions~~) and performance parameters/indicators (e.g. yield, chromatographic profiles) should be appropriately evaluated.	Agreed.
255	7	**Comment:** The terms "Performance Parameters/Indicator" are mentioned but not defined or differentiated, which may lead to different interpretations. **Proposed change:** Make the text consistent with regard to the terms "process indicator, Performance indicator, Performance parameter" in lines 99, 207.	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
255	7	**Comment:** Typo- please delete one of two "conditions". **Proposed change:** "…e.g. column loading capacity, flow rate, length, elution/washing conditions ~~conditions~~) and performance …"	Typo corrected.
257-260	6	**Comment:** It is not clear whether this paragraph is referring to automation. If so could it be stated? In case it refers to automation it should be applicable to the upstream process as well. **Proposed change:** Move this paragraph so it is applicable to both upstream and downstream process and clarify if it is intended for automation validation.	Reference to feed forward and feed back loop systems has been removed from the guideline due to limited experience.
257-260	6	**Comment:** It is unclear what feed forward or feedback loops means in the context process (e.g. does this apply specifically to processes using PAT or to any process step in which forward processing allows an adjustment to stay within a range). It would be beneficial if an example is provided of a situation using feed forward or feedback loops. It is also not clear why this particular process situation requires a study to ensure the process is "verified according to an approved protocol" where this is not required almost anywhere else in the process evaluation part. **Proposed Change:** Please add clarification and examples, if possible.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
257-260	6	**Comment:** We suggest to include a similar sentence in 6.2.2 **Proposed change:** Move part of the paragraph to 6.2.2. Verification of downstream process.	See above. The text has been deleted.
259-260	6	**Comment:** "Design of experiments" can be seen as one out of many statistical methods which can be applied in order to investigate the effect of a parameter variation. The sentence could be interpreted as a requirement to use DoE and thus excluding any other method. "Design of experiments" could be clarified by adding "(DoE, another statistical based approach or a calibrated mechanistic model) -" **Proposed change:** In the case where feed forward and/or feedback loop systems are used to accommodate the conditions of process steps, all claimed conditions should be appropriately evaluated regarding their impact on output material(s), according to an appropriate design of experiments **(DoE, another statistical based approach or a calibrated mechanistic model)**, and verified…..	See above.
261-268	2	**Comment:** Reference to an "approved protocol" is confusing in the stated context. It needs to be clarified as to whether this would require prior approval by the Agency or by the appropriate Quality Unit. If the former, this would be an additional regulatory burden and an escalation of current requirements which is not aligned with the upstream	The very last words have been changed to "*in accordance with a protocol approved at the time of MAA*". It should be noted that this is not considered as an escalation of requirements.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		requirements. If the latter (approval needed by the Quality Unit), then the text is unnecessary as ICH Q7 guidance states that the Quality Unit is responsible for: "Reviewing and approving validation protocols and reports". On this basis the proposal is to remove the reference to an approved protocol. The alternative would be to clarify the meaning of an approved protocol in this context. This seems like a critical observation to the team. **Proposed change:** [Line 265-268]: "Considering the number of purification cycles required for this evaluation, small scale studies are considered appropriate to estimate and set the maximum number of cycles at the time of regulatory submission, provided that full scale verification is performed on an ongoing basis, to confirm the column performance and integrity~~, in accordance with an approved protocol~~."	
263-265	1	**Comment:** If absence of specific leaching studies is appropriately justified, this should not be limited only to resins with small molecule functional group. **Proposed change:** Absence of specific leaching studies may be acceptable, but requires appropriate scientific justification.	Agreed. "small molecule functional group" has been removed.
263-265	4	**Comment:** It is scientifically unclear why the absence of studies may be acceptable for resins with small molecule functions groups, while such studies are apparently obligatory for large molecule functional	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		groups. Clarification should be considered.	
265-267	12	**Comment:** We propose to modify the sentence as follows. "*Small scale studies or studies performed on products with comparable physico-chemical and biological properties and operating conditions are considered appropriate to estimate and set the maximum number of cycles at the time of regulatory submission ….*"	Not agreed as a general principle due to difficulties to justify validity of extrapolation.
265-268	6	**Comment:** We propose to change this paragraph to encompass the two different scenarios; viral clearance cycles and other cycles. Since several changes are proposed, no "track changes" are included. **Proposed change:** Considering the number of purification cycles required for this evaluation, small scale studies are considered appropriate to initially estimate the maximum number of cycles at the time of regulatory submission **(except for viral clearance purification cycles),** provided that full scale verification is performed on an ongoing basis, to confirm the column performance and integrity, in accordance with an approved protocol. **For viral clearance purification steps, the maximum number of cycles must be determined in small scale at the time of regulatory submission and for additional extensions in maximum numbers of cycles determined in small scale in accordance with an approved protocol.**	Number of cycles and viral clearance are distinct issues. For evaluation of viral safety, reference is made in the guideline to ICH Q5A.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
265-268	10	**Comment:** Current industry practice is full scale verification is performed near the end-of-life of the column, which was estimated and established at small scale. **Proposed change:** Considering the number of purification cycles required for this evaluation, small scale studies are considered appropriate to **initially** estimate ~~and set~~ the maximum, number of cycles at the time of regulatory submission **(except for viral clearance purification cycles)**., provided that full scale verification is performed on an ongoing basis to confirm the column performance and integrity, in accordance with an approved protocol. **For viral clearance purification steps the maximum number of cycles must be determined in small scale at the time of regulatory submission and for additional extensions in maximum numbers of cycles determined in small scale in accordance with an approved protocol.**	See above.
267-268	1	**Comment:** Based on the manufacturing practice, the definition of a maximal number of cycles is not an appropriate indicator for the column performance and integrity. Instead, process control parameters such as IPCs are adequate to reflect the column performance. **Proposed change:** Alternatively, the column performance can be confirmed by monitoring product and/or process-related impurities against predefined acceptance criteria e.g. by appropriate in process	Proposed rewording not agreed since in-process controls as such would not detect changes in separation performance of the columns. The guideline gives the standard way of showing this, other possibilities exists if appropriately justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		controls.	
267-268	6	**Comment:** In regards to the column lifetime statement of “in accordance with an approved protocol”, please indicate whether or not this type of ‘column performance and integrity testing protocol’ needs to be provided in the MAA?	See above.
270	6	**Comment:** We propose to revise sentence to encompass intended modifications to the molecule, too. **Proposed change:** Verification activities should confirm the ~~clearance capacity~~ **intended performance** of the entire downstream **process (e.g., regarding purity, impurity clearance, intended modifications)**,….	Agreed.
270-272	1	**Comment:** The terminology needs to be consistent across the document, NOR is used in the upstream section but normal acceptable range is used in the downstream section.	The term “NOR” was removed from the text.
270-272	2	**Comment:** These lines include the statement: “Verification activities should confirm the clearance capability of the entire downstream process, showing that process parameters and performance indicators - in accordance to normal acceptable ranges”. The terminology needs to be consistent across the document, NOR is used in the upstream section but normal acceptable range is used in the downstream section.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Use NOR throughout the document.	
271	6	**Comment:** Clarify sentence and avoid “performance indicators” as it may be misunderstood, and replace by “output” **Proposed change:** “Verification activities should confirm the clearance capability of the entire downstream process, ~~showing that process parameters and performance indicators - in accordance to normal acceptable ranges - are able~~ to consistently generate the targeted quality of process intermediates and active substance (i.e. appropriate purity/impurity profile for the given stage). **This should be supported by in-process testing results of process parameters and process outputs.”**	Agreed.
275-276	2	**Comment:** “For biological products, these situations are usually restricted to some refiltration or re-concentration steps upon technical failure of equipment.” The team has suggested to add human error causes where justified. **Proposed change:** “For biological products, these situations are usually restricted to some refiltration or re-concentration steps upon technical failure of equipment or identified human error”.	Since the root causes for the need for reprocessing need to be identified to be able to design a validation study to justify the reprocessing, human errors in general cannot be mentioned since this may cover any error.
275-277	1	**Comment:** Not only technical failure of equipment is a root cause for reprocessing. Personal failure is for example another root cause. In addition, concurrent	See above. A protocol of ongoing process verification is useful for large scale verification but small scale data is required for initial approval of reprocessing option.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		validation should be allowed in case of reprocessing, because under normal circumstances these events happen seldom. **Proposed change:** For biological products, these situations are usually restricted to some refiltration or re-concentration steps and/ or predefined operations. These steps should be appropriately described in the regulatory submission. Reprocessing should be validated e.g. on a concurrent basis.	
275-281	6	**Comment:** dd the possibility to use small scale models for reprocessing after equipment failure in filtration and re-concentration **Proposed change:** Add in line 280: "This demonstration can be done at commercial scale or with appropriate small scale models".	Agreed.
275-277	7	**Comment:** As also other reasons for failures may exist, like errors made by man, we would propose here to describe "technical failure" as one example only. **Proposed change:** "For biological products, these situations are usually restricted to some refiltration or re-concentration steps**, e.g.** upon technical failure of equipment.	Not agreed. This is outside the scope of the guideline.
275-281	7	**Comment:** Add the possibility to use small scale models for reprocessing after equipment failure in filtration and re-concentration. **Proposed change:** Add in line 280: "**This**	Agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		demonstration can be done at large scale or by using appropriate small scale models".	
276	7	**Comment:** Reprocessing should not be restricted to filtration. For example, also flow-through chromatography and membrane adsorbers can be readily reprocessed, e.g. after failed gel bed integrity. Therefore, robustness of the step should be the justification for reprocessing. **Proposed change:** "…these situations are usually restricted to ~~some refiltration or re-concentration steps~~ **selected steps with robust performance, e.g.** upon technical failure of equipment …"	Mechanical breakdown of a chromatography column has been included as another example.
276	6	**Comment:** It could be anticipated that in some case, reprocessing for a given purification column is conducted because of inadequate packing of the column. Furthermore, it would be valuable to further expand the concepts of evaluation / verification / ongoing verification in the case of reprocessing, where it could be anticipated that the possibility of reprocessing is properly evaluated in the MAA, accompanied with a verification protocol (including the conditions of potential reprocessing). **Proposed change:** For biological products, these situations **are mostly related (but not limited)** ~~usually restricted~~ **to** some refiltration or re-concentration steps upon technical failure of	The section on reprocessing has been rewritten.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		equipment. These steps should be appropriately described and validated in the regulatory submission. Such documentation should include the ~~demonstration~~ **evaluation** that the reprocessing step(s) do(es) not impact the quality of the active substance. ~~and~~ **The approach considered to verify the absence of impact could include a proposal of controls that will be applied and a** description of conditions for which reprocessing could ~~be applied~~ **occur** (e.g. equipment failure). An essential prerequisite for the acceptance of a reprocessing step is the clear~~ly~~ identifi**cation** ~~ed~~ **of the** root cause.	
277-278	6	**Comment:** Minor correction of sentence proposed **Proposed change:** These steps should be appropriately ~~described and validated~~ **validated and described** in the regulatory submission.	The section on reprocessing has been rewritten.
283-286	6	**Comment:** In case the small scale model is fully representative of the proposed commercial scale process, it could also be used to demonstrate/justify the hold times. **Proposed change:** Where hold times or storage are applied to process intermediates, the impact of the hold times and conditions on the product quality should be appropriately evaluated. The evaluation should be conducted as real-time, real-conditions studies, usually on commercial scale material. However, small scale studies	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		could ~~additionally~~ **alternatively** be considered if appropriately justified.	
284-286	2	**Comment:** The statement "The evaluation should be conducted as real-time, real-conditions studies, usually on commercial scale material. However, lab-scale studies could additionally be considered if appropriately justified" could be usefully reworded. **Proposed change:** Re-wording to describe both chemical and microbial stability studies.	The need to study both structural and microbial aspects is highlighted in the text.
285-286	1	**Comment:** Lab-scale studies should be an alternative, if appropriately justified. **Proposed change:** However, lab-scale studies could alternatively be considered if appropriately justified. Also recommend wording to describe both chemical and microbial stability studies.	"alternatively": Agreed (see above) Chemical/microbial: see above)
285-286	4	**Comment:** The *sentence 'However, lab-scale studies could additionally be considered if appropriately justified'* is unclear. The sentence itself states that this is an additional requirement, although the context suggests that such lab-scale studies may replace real-time real-scale studies. Deletion of the word 'additionally' or clarification should be considered.	Agreed. See above.
285-286	10	**Comment:** Full scale study is required for microbial hold, but worst-case small scale studies would be sufficient to establish chemical stability. The word 'Additionally' may be interpreted as both full-scale and	"additionally" replaced with "alternatively" (see above).

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		small scale studies are required. **Proposed change:** However, lab-scale studies could ~~additionally~~ be considered if appropriately justified.	
286	7	**Comment:** Appropriate hold time studies can partly also be done using smaller scale. E.g., when intermediates are used from large scale they can be processed at small scale to come up with representative data. **Proposed change:** Delete “additionally” in line 286: “However, lab-scale studies could ~~**additionally**~~ be considered…” Alternatively add in line 286: “**It is not expected that all evaluations are performed at large scale, e.g. for some studies intermediates from large scale can be processed at small scale**”.	See above.
288-289	6	**Comment:** The request of justifying the maximum hold time for each step may be misleading, as hold time may not be claimed for all individual steps. **Proposed change:** “…in order to justify a maximum hold time **claimed** ~~for each process step~~.”	Agreed.
290-291	14	**Comment:** The simple thermal analysis experiments provide insight into complex biological problems guide and drive new directions in evaluation of	Not agreed as thermo-analytical techniques are only one of the approaches to study this and the guideline is not intended to describe how studies should be performed.

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		biotechnological products. **Proposed change:** *"Studies **via thermo-analytical techniques** conducted under worst case conditions and/or abnormal conditions (e.g. higher temperature, longer time) could be used to further support the suitability of the claimed conditions."*	
292	12	**Comment:** Cumulative hold time may not be adapted for vaccines processes since some vaccine intermediates are not characterisable.	The underlined text has been added: "*Provided the intermediate is stable and allows meaningful analyses, independent studies of individual steps are likely to be sufficient and cumulative studies are not considered necessary.*"
292-294	11	**Comment:** Consider to include examples for cases in which hold time studies, studying of worst case conditions and conduct of cumulative hold time studies is considered dispensable.	Examples have not been included to limit the level of detail on this point.
293	6	**Comment:** Add clarity **Proposed change:** add "…analyses**, independent** studies of **individual** steps are…"	Agreed.
295	8	**Comment:** Shipping and transport validation. Annex 15 EU GMP describes shipping and transportation verification rather than validation. **Proposed change:** Verification seems more appropriate since transportation has a high degree of variability and cannot really be validated in the true	Agreed. "Validated" has been replaced with "verified".

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		sense.	
295-298	1	**Comment:** PDA tech report 39 - review rationale and suggest alignment by EMA	Validation of shipping and transportation is mainly covered under GMP and the issues raised in the section only deals with aspects that relate to the data to be submitted in connection to applications. Widening of description is therefore not considered necessary.
295-298	2	**Comment:** The statement "Shipping and transportation of intermediates and active substance should be validated…", could usefully take more account of existing information. **Proposed change:** Review the PDA tech report 39 - review rationale and increase level of alignment in this guidance.	See above
295-298	6	**Comment:** We suggest to modify sentence to clarify the expectations. **Proposed change:** Shipping and transportation conditions of intermediates and active substances should be evaluated. It should be demonstrated that the quality of the intermediates or active substance will not be altered **beyond acceptable limits** if transported according to the defined conditions. A short summary should be provided in the dossier.	Comment captured by rewording stating that quality of the intermediate or active substance should be maintained during transport. This quality will be defined by acceptance criteria and hence no need to spell this out in isolation.
295-298	6	**Comment:** Shipping and transport routes and conditions in the supply chain cannot be validated as they are never 100% repeatable due to many variables	"Validated" has been replaced with "verified". The other proposals for rewording are considered redundant.

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		that are not constant like e.g. weather, different vehicles (trucks, ships, airplanes), drivers, pilots, load patterns, containers (ship containers, air containers). They can only be systematically checked in order to show the robustness of the system used. In justified cases, it may not be possible to provide full scale data at the time of submission. In such cases a respective monitoring plan should be provided. **Proposed change:** Shipping and transportation of intermediates and active substance should be ~~validated~~ **qualified**. ~~Such study~~ **Data** should ~~include~~ **provide** demonstration that the quality of the intermediate or active substance will not be altered if transported according to the defined conditions. A short summary of the ~~study~~ **monitoring results** should be provided in the dossier. **In justified cases, a monitoring protocol may be included.**	
295-298	7	**Comment:** As the final secondary packaging/configuration is usually available at a very late stage in development, this requirement may unduly delay filings and access of patients to medicines. In the context of a risk based approach we propose that an appropriate protocol should be sufficient for inclusion in the dossier. **Proposed change:** "A short summary of the study should be provided in the dossier**. Alternatively, in the context of a risk based approach it is possible**	Not agreed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to include an appropriate protocol for the validation of shipping and transportation in the dossier instead of a completed study".	
297-298	11	**Comment:** Consider to include reference to dossier section at the end of the sentence. **Proposed change:** A short summary of the study should be provided in the dossier **(section 3.2.S.2.2)**.	Not agreed. Location of information in the dossier is an issue beyond this guideline. Only general references to CTD sections have been included in the text.
303-304	10	**Comment:** Comparable outputs may not always be achieved using the same input ranges due to differences in manufacturing technologies requiring various control strategies. **Proposed change:** "The adapted process should be capable of achieving comparable outputs. ~~when operating within the same input ranges~~"	Agreed.
306	10	**Comment:** Considering lifecycle approach of process validation, it is not clear what documentation would be required to satisfy "it must be demonstrated that the subsequent site has reached a validated state." **Proposed change: "...**it must be demonstrated that ~~that the subsequent site has reached a~~ **the process is** validated ~~state~~ **at a subsequent site**.	The line break between lines 306 and 307 has been removed and the text explains what is meant with "reached a validated state".
307-316	1	**Comment:** Inclusion of an upstream example is recommended here.	An example has been included.
307-316	2	**Comment:** Regarding the statement "The relevance of previous validation studies should be discussed…..", it	An example has been included.

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		would be useful to include an upstream example. **Proposed change:** Include an upstream example.	
308	7	We appreciate the clarification that there is normally no expectation to re-evaluate the complete process.	Noted.
308-310	7	**Comment:** A perspective for the use of a process design space is given. Frequently, supply for market requires multiple production sites or lines in order to fulfil market and patient demands. Process evaluation studies should be designed in a way that all adaptations between different production sites or lines are fully understood upfront and already described in the MAA/BLA. As a result, post-approval changes can be avoided. **Proposed change:** Add: "Process evaluation studies may be designed in a way that they cover minor process adaptations required to enable manufacturing at multiple sites or different scales".	The text as proposed in the guideline allows for a design that may cover also certain adaptions to be applied at future sites and the proposed text is not included. It is understood from the comment that the intention would be to avoid post approval changes. Adding a new site will however need a submission for variation according to the variation regulation.
309-310	11	**Comment:** Reference to matrixing/bracketing as an adequate approach to reduce number of validation batches for active substances produced from rare/valuable starting materials (e.g. human plasma) should be inserted best including an example. If accepted as proposed, the respective definitions should be included in the 'Definitions' section (starting at line 317).	Matrixing (e.g. not to test everything at the same time) /bracketing (e.g. different strengths) are rare events for drug substance validation and therefore not mentioned as such in the guideline. The principles would apply if sufficiently justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: *"Nevertheless, process verification studies would be expected to be part of the submission,* ***a bracketing or matrixing approach may be used.****"*	
313-316	1	**Comment:** Process optimisation/changes should be assessed taking into consideration the impact of change in the quality of the active substance. The potential impact on quality and comparability studies should be performed in order to demonstrate the equivalence of quality of the active substance before and after process optimisation. **Proposed change:** In case of optimisations of the production by using new processes (e.g. addition of new purification steps, replacement of one step with another (such as size-exclusion chromatography with ion exchange chromatography)) comparability on quality of the drug substance should be demonstrated by appropriate comparability studies.	Addition text has been included regarding site-specific adaptation of the process.
313-316	2	**Comment:** The stated example could be interpreted such that all buffer condition changes will require a new marketing authorisation when in fact these can be minor in nature, where appropriately justified. The team proposal is to remove this example but an alternative might be to specify this more clearly to allow appropriate flexibility of interpretation. Additionally, the team think applying a risk based approach in evaluating manufacturing changes and regulatory pathways would be helpful.	The example on "different conditions in buffers" has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: "Optimisations of the production by using new processes (e.g. addition of new purification steps, replacement of one step with another (such as size-exclusion chromatography with ion exchange chromatography), ~~different conditions in buffers~~) is considered to constitute an alternate process and is not allowed within the same marketing authorisation."	
313-316	6	**Comment:** Delete the example "different conditions in buffers" as this may depend on the function and criticality in the process. In addition we propose to add some flexibility in this paragraph to allow the option of using the agency scientific advice to accommodate potential optimisations that may not be as simple as filters and not as drastic as a change in purification steps. **Proposed change:** Optimisations of the production by using new processes (e.g. addition of new purification steps, replacement of one step with another, such as size-exclusion chromatography with ion exchange chromatography) ~~different conditions in buffers)~~ **may be** ~~is~~ considered to constitute an alternate process and ~~is~~ **may** not **be** allowed within the same marketing authorisation. **It is encouraged to seek CHMP Scientific Advice in case of such changes**.	Agreed.
313-316	6	**Comment:** This section appears not to completely reflect all options and may lead to misunderstanding. E.g. processes operated in more than one facility can	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be optimized at all sites in parallel. The current wording may give the impression that no process optimization is allowed. **Proposed change:** Add: "Process optimisations per se are allowed if appropriately justified by the sponsor and approved by authorities. If more than one production site is used it needs to be ensured that processes between sites remain harmonized, e.g. to avoid that two different processes are running in parallel."	
313-316	7	**Comment:** This section appears not to completely reflect all options and may lead to misunderstandings. E.g. processes operated in more than one facility can be optimized at all sites in parallel. The current wording may give the impression that no process optimization is allowed. **Proposed change:** Add: "Process optimizations per se are allowed if appropriately justified by the sponsor and approved by authorities. If more than one production site is used it needs to be ensured that processes between sites remain harmonized, e.g. to avoid that two alternate processes are running in parallel".	Agreed. See above.
313-316	7	**Comment:** A change in buffer is not considered to be a good example as the impact depends on its use in the process. It is proposed to delete this example from the text.	Agreed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change:"… chromatography with ion exchange chromatography), ~~different conditions in buffers)~~ is considered to …"	
315	6	**Comment:** editorial change to improve clarity/readability. **Proposed change:** different **buffer** conditions ~~in buffers~~).	The example on "different conditions in buffers" has been removed
317	8	**Comment:** Suggest incorporating a definition for "small scale" **Proposed change:** Small scale batches are any scale smaller than full scale commercial batch size e.g. pilot scale, or lab scale.	Agreed.
317	4	**Comment:** Glossary: For the sake of clarity and ease of reference, the definition of PAR (as stated in ICH Q8) could be repeated in the glossary, because it is a key concept of this guideline. A definition for the closely related concept NOR is given, and several other definitions (e.g. for control strategy) are repeated from other guidelines.	The ICH Q8 definition of PAR has been added. The term NOR has been removed from the guideline.
317	7	**Comment:** For clarity, please add PAR definition according to ICH Q8 with an addition according to the PDA Technical Report no. 60 - Process Validation: a Lifecycle Approach, 2013, ISBN: 978-939459-51-3. **Proposed change:** Please add: "Proven Acceptable Range (ICH Q8): A characterised range of a process parameter for which operation	The ICH Q8 definition of PAR has been added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria." "Additionally it is also applicable to determine the proven acceptable range by using multidimensional combination of input parameters or process parameters as well".	
317	9	**Comment:** Please add the PAR in the definitions.	The ICH Q8 definition of PAR has been added.
317	10	**Comment:** There is no definition of proven acceptable range (PAR) or reference to the definition. Some may not be familiar with the term. **Proposed change:** PDA recommends adding the ICH Q8(R2) definition of PAR to the glossary.	The ICH Q8 definition of PAR has been added.
317	9	**Comment:** Please add the hold time definition.	A definition of hold time has been added.
317	11	**Comment:** Amend 'Definitions' section by adding definitions for the terms listed below) • commercial scale (batch) • small scale versus (used several times throughout the document) versus scale-down (line 249) **Proposed change:** Shift definitions for 'continuous process verification' (318-320) and 'ongoing process verification' (340-341) down listing them after the definition of 'process verification (355-358) consider to	A definition of small scale has been added. The definitions are presented in alphabetical order.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provide a clearer demarcation of ongoing versus continuous process verification.	
327-328	7	**Comment:** Please add examples for clarity. **Proposed change:** Please add examples for “feedback”, “feed forward” and “feed forward and/or feedback loop”.	Reference to feed forward and feedback loop systems has been removed from the guideline due to limited experience.
327-330	13	**Comment:** A clarification is proposed because of lack of clear differentiation between two terms presented in the section “Definitions”. **Proposed change:** Feedback - the modification or control of a process or a system based on its results and effects <u>that uses information from measurements to manipulate a variable to achieve the desired result</u>. Feed forward – the modification or control of a process or a system ~~using its anticipated results or effects~~ based on predicting of the effects of measured disturbances and taking corrective action to achieve the desired result.	Reference to feed forward and feedback loop systems has been removed from the guideline due to limited experience.
333	7	**Comment:** High Impact Model is not mentioned in the text. **Proposed change:** Delete the definition of “high impact model”.	The definition “high impact model” has been removed.
333-335	13	**Comment:** No reference in the text is made to the definition of “High-impact model”. It is suggested to	The definition “high impact model” has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		delete this term from “Definitions” or to make an adequate reference in the guideline.	
336-339	7	**Comment:** The definition of NOR given in the current draft guideline says: “typical operational variability”, that is, in our opinion less practical and precise wording, compared to the definition that is given in the PDA Technical Report no. 60 - Process Validation: a Lifecycle Approach, 2013, ISBN: 978-939459-51-3: **Proposed change:** “The NOR ~~describes a region around the target operating conditions that contains typical operational variability and is within the claimed acceptable ranges.~~ **is a defined range, within (or equal to) the claimed acceptable range, specified in the manufacturing instructions as the target and range at which a process parameter is controlled, while producing unit operation material or final product meeting release criteria and CQAs**. As such NORs themselves are not expected to be submitted in the dossier for a biological product.”	The term “NOR” was removed from the text. “Normal set point” is used instead.
336-339	10	**Comment:** In PDA’s experience, NORs are submitted as part of the verification studies, as noted in section 5.2. PDA recommends deleting reference to submission requirements in this definitions section. PDA would also like to suggest a more specific definition as taken from Technical Report 60 “ **Proposed change:** Replace the current definition with	The term “NOR” was removed from the text. “Normal set point” is used instead.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the following: A defined range, within or equal to the Proven Acceptable Range specified in the manufacturing instructions as the target and range at which a process parameter is controlled while producing unit operation material or final product meeting release criteria and Critical Quality Attributes.	
337-338	1	**Comment:** This implies target operating conditions are different from NORs but Target operating conditions are not defined in the glossary. Would suggest that use the term target initially, then based on a sufficient dataset, these should become becomes NORs.	The term “NOR” was removed from the text. “Normal set point” is used instead.
337-338	2	**Comment:** In the definitions there is the statement “The NOR describes a region around the target operating conditions that contains typical operational variability and is within the claimed acceptable ranges”, implies target operating conditions are different from NORs but Target operating conditions are not defined in the glossary. **Proposed change:** The team would suggest that organisations might be advised to use the term target initially, then based on a sufficient dataset, these should become becomes NORs.	The term “NOR” was removed from the text. “Normal set point” is used instead.
337-339	12	**Comment:** We propose to delete the last sentence which is not a definition.	The term “NOR” was removed from the text. “Normal set point” is used instead.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
338	6	**Comment:** There should be clarification of the need for submission of NORs. Line 338 states that NORs do not need to be provided in the dossier while there might be an expectation to include those in section 3.2.S.2.5 of the MAA to describe process verification. **Proposed change:** Provide clarity in the definition that NORs do not need to form part of the registered detail in S2.2/S2.4. Reference is also made to our General Comments.	The term “NOR” was removed from the text. “Normal set point” is used instead.
340	6	**Comment:** It would be helpful to mention that Ongoing process verification is also referred to as “continued process verification” in other regions to avoid misunderstanding. **Proposed change:** “ongoing **(continued)** process verification”	Agreed.
340-341	2	**Comment:** Definition for ongoing process verification can be improved. **Proposed change:** Propose the definition be changed to “Documented evidence of the continued capability of the process and controls to produce product that meets the desired quality through the commercial lifecycle of the product.”	Not agreed. The definition is in line with other EU guidance.
355-358	7	**Comment:** Please add clarification according to line 153-154. **Proposed change:** Add:	The term “NOR” was removed from the text. “Normal set point” is used instead.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Such studies are generally performed in accordance to the expected normal operating ranges (NORs)".	
359	7	**Comment:** Directive 2001/83/EC is missing on the reference list. **Proposed change:** Please add to the reference list: Directive 2001/83/EC.	The reference has been added.
359	6	**Comment:** Please include a reference to EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1 Guideline on process validation for finished products - information and data to be provided in regulatory submissions	The reference has been added.
359	6	**Comment:** Please include a reference to the updated GMP Annex 15 when final.	The reference has been added.
359	3	**Comment:** Use of statistics for process evaluation and verification is not noted. **Proposed change:** Include references to relevant guidelines.	Not agreed. Statistics is outside the scope of this guideline.
359	8	**Comment:** ICH 11 refers to ICH 8. **Proposed change:** Suggest incorporating ICH Q 8 in the reference list.	Agreed.
360	7	**Comment:** In line 320 ICH Q8 is mentioned and missing from the reference list.	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please add to the reference list: ICH Q8 (R2) Pharmaceutical Development	