EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Submission of comments on 'Guideline on process validation for finished products - information and data to be provided in regulatory submissions' (EMA/CHMP/CVMP/QWP/70278/2012-Rev1)

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

Stakeholder number	Name of organization or individual
1	Spanish Association of Pharmacists in Industry (AEFI)
2	IFAH Europe
3	IPFA
4	Fabbrica Italiana Sintetici S.p.A (FIS)
5	SciencePharma
6	Plasma Protein Therapeutics association (PPTA)
7	AOP Orphan Pharmaceutical AG
8	Association of the European Self-Medication Industry (AESGP)
9	Parenteral Drug Association (PDA)
10	Association of the Pharmaceutical Industry in Norway (LMI)
11	Bristol-Myers Squibb (BMS)
12	ALK-Abello
13	Institution of Mecanical Engineers (IMechE)
14	Orion
15	Kinapse Ltd.
16	GE Healthcare Ltd. (GEH)
17	European Federation of Pharmaceutical Industries and Associations (EFPIA)
18	International Society for Pharmaceutical Engineering (ISPE)
19	Merck Sharp & Dohme (MSD)
20	Bausch & Lomb
21	Apotex
22	Shire Human Genetic Therapies
23	Norgine

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	No comments	
2	No comments - supports	
3	No comments - supports	
4	The guideline does not apply to manufacturers of active ingredients, but is said to report useful information. This approach introduces uncertainty and arbitrariness in the application of the principles outlined by the guideline for API manufacturers, leaving the freedom for inspectors and auditors to present different expectations. Since the guideline appears to be applicable also to API manufacturer, it should be written to cover also such operations.	Point noted: this note for guidance is intended to apply to data submitted in the MA dossier. Only data generated to validate the manufacturing process of the intended commercial dosage form is requested in the dossier. For this reason, data generated to validate the active substance manufacturing process is not part of the scope.
4	Process deviations, out of trends and atypicals, when adequately investigated, provide information that is often more significant than a simple 3-batches process validation study, providing an increased assurance of process knowledge and robustness. This should be reported as a core element of the continued process verification.	Point noted: process deviations, out of trends and atypicals are indeed important quality indicators. They are core element of GMP and quality systems rather than core elements of continued process verification. Therefore will not be included in this guideline.
5	According to both the Directive 2001/83/EC as amended (Annex I, part 1, section 3.2.2.3.) and the Directive 2001/82/EC as amended (Annex I, part 2, section B) *"experimental studies validating the manufacturing process"* should be included in the marketing authorisation dossier *"where a non-standard method of manufacture is used or where it is critical for the*	Comment not agreed: it is not possible to list all cases where manufacturing processes are critical for products. Each should be reviewed on a case by case basis.

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	product". The draft of the guideline lists non-standard methods of manufacture, however cases where manufacturing processes are critical are not systematically discussed (biological / biotech products (lines 116-117) are given as examples only). It is hence proposed to list all the cases of manufacturing processes being critical for products.	
5	For those cases when process validation is required at the time of submission (anticipated by both Directives 2001/83/EC and 2001/82/EC), it is proposed to systematically discuss basic validation requirements in terms of batch size and number of batches as it was discussed in the draft guideline (lines 121-127). Of particular importance is when validation studies included in the dossier may in part come from pilot scale batches.	Point noted – no response required.
5	In the case of validation mode (traditional process validation or continuous process verification) section 5.3. *"Hybrid approach"* states that for *"non-standard processes (as defined in section 8) the process validation requirements highlighted in section 5.1* [i.e. traditional process validation] *should be applied unless otherwise justified"* (lines 189-190). In introduction to section 8 it is stated however that the section is *"only relevant for processes which have not been validated using continuous process verification"* (lines 229-230). It is proposed to clarify whether CPV approach may be applicable to non-standard processes (and manufacturing processes being critical for products) and, if relevant, to systematically clarify conditions.	Comment agreed: continuous process verification may be applied to any type of process: standard, non-standard, specialized, etc. Section 5.3 has been amended.

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6	In order to facilitate global drug development and alignment with other regulatory agencies, the concepts of process design, process qualification and continued process verification should be described (for alignment with the FDA guidance)	Comment not agreed: due to regional regulations it is not envisaged to align and harmonize approaches between EU and FDA guidelines. Actually, FDA guidance is aimed at GMP inspectors and industry while EU guideline is aimed at quality assessors and industry.
6	Some processes listed as "non standard" are standard for some companies in view of their long experience and mastery with these processes used for numerous products and approved in Europe years ago. It is essential that companies can classify them as standard with a justification and provide data as necessary to demonstrate that the process is under control and product quality is met consistently. Examples: lyophilisation, preparation of emulsions, preparation of products with drugs in low content	Point noted – companies can justify that a product or process is 'standard' for them. Section 8 has been updated accordingly.
6	The use of almost identical terms "*Continuous Process Verification*" and "*Continued Process Verification*" defining different requirements risks being a source of confusion for pharmaceutical manufacturers and also between authorities and manufacturers. Although the definition for "Continuous Process Verification" is part of harmonization (ICH Q8) it is not used in important agency validation guidance documents published recently. We propose that these discrepancies should be resolved before the Guidance is becoming effective to establish a harmonized approach with ICH.	Point noted - continued process verification has been amended to 'on-going process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
7	Tablets and capsules production using conventional mixing and granulation procedures (additional for tablets: compressing procedures)are considered as	Point noted: no specific comment made, however this would be acceptable under the current wording in the guideline. This would be acceptable for dossier submission, but may not cover all GMP

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	standard manufacturing processes and we propose using 1-2 production scale batches and 1 pilot scale batch for the process validation.	requirements.
8	Risk assessment is not mentioned in this new guideline. Is it no longer recommended to perform a risk assessment for process validation?	Point noted: it is still recommended to perform a risk assessment for process validation. Continuous process verification is a science and risk-based real time approach. Risk assessment is also required in GMP annex 15.
9	Comment: The Executive Summary of this guideline states, in part,*"...The guideline is brought into line with ICH Q8, Q9 and Q10 documents and the possibility to use continuous process verification... and clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality system as described by ICH Q8, Q9 and Q10."* PDA fully supports a revision of the guideline to meet those goals. However, we note that the definition of Process Validation in the guideline remains the same definition described in EU GMP Annex 15, Validation and Qualification. This definition dates from 2001 and reflects the understanding and conduct of process validation before the advent of the referenced harmonised ICH quality guidelines. Recommendation: For the above reason, and consistent with the goal of international harmonization of regulatory guidance, we suggest the EMA consider adoption of an updated	Comment not agreed: the definition of process validation is unchanged. Indeed, ICH guideline did not bring a new definition to process validation, but rather an alternative in terms of methodology and approval. On the other hand the objective of the revision is to offer two options depending on the development strategy. The traditional approach and the enhanced approach. This is the rationale for keeping the process validation section and adding a new section for the alternative approach. The definition used by FDA in their revised process validation guideline cannot be adopted in the EU guidance due to regional regulation indeed validation guidance concern GMP inspectors at FDA level while validation guidance is aimed at assessors at EU level.

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	definition of Process Validation which captures the benefits of ICH Q8, Q9, Q10. A starting point for consideration is the definition used by FDA in their revised process validation guidance published in January 2011 and which does capture the ICH concepts, to promote language consistency. We would like to also note that portions of the FDA definition are also used in the text of ICH Q11.	
9	Comment: The guidance mentions that information on process validation should be included in the dossier (e.g. Module 3) but does not describe which section should be used. For example, in the EU CTD information about process validation (drug product) can be provided in the following sections: - 3.2.P.2.3 Manufacturing Process Development; Feasibility of Continuous process verification strategy (line 167), Hybrid (line 186), production scale data (line 238) - 3.2.P.3.5 Process Validation and/or Evaluation - 3.2.R Process Validation Scheme for the Drug Product (EU regional part). Recommendation: We believe it will be helpful to both assessors and applicants if the guidelines for preparing eCTD submissions provide clear guidance on which section process validation data should be presented. Alternatively, the specific Process Validation guideline could be modified to give clear recommendations	Comment not agreed. The reference to specific sections is part of CTD guidance (ICH M4) and should not be reported in this guidance.

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	regarding which sections of the dossier are preferred for the placement of validation information.	
10	General comment when viewed in the context of the corresponding FDA Guidance for Industry document: • It would be beneficial for terminology to be aligned across the EMA and FDA documents. The basic requirement for and scope of Process Validation is effectively the same, however the two sets of guidance use different terminology to mean the same thing. • As these documents are likely to lead to further independently generated guidance for industry (eg ISPE), further harmonisation of terminology would be welcome. The EMA guidance is not directly relevant to API manufacture, whereas the FDA guidance is applicable to API manufacture.	Point noted. Efforts have been made to harmonise terminology between EU guidance and FDA guidance however due to differences in regional regulation (see above) it is not possible to harmonise further. On the other hand it is reminded that the guideline addresses data to be included in the dossier. Since validation data related to non-sterile API is not requested in the dossier the EMA guidance is not relevant for non-sterile API.
10	Other general observations: • Little emphasis on use of statistical expertise and tools, unlike FDA guidance which places much emphasis on this expectation. Science and risk based approach needed, but no specific guidance on expectations. Little or no guidance on application of quality risk management, although it is expected.	Point noted: statistics to be used should be proposed and justified by the applicant. No guidance on statistical tools will be given in the guideline. ICH Q9 is referenced in the guideline. This guideline should be read in conjunction with ICH Q8, 9 and 10.
11	Overall this guidance is well written. Some clarifications are required to avoid confusion. They are captured below along with additional suggestions for the modification of the text	No specific comment to be addressed.
12	Section 5.2 in particular appears as very general	Point noted: justifications should be provided on a case by case basis

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	(concept paper stage) and do not allow manufacturers to assess the extent of justifications to provide in order to use the CPV approach.	by the applicant. No general guidance on the acceptability of justifications can be given.
12	There is a strong resemblance between the name for the two described concepts - Continuous Process Verification (CPV) - Continued Process Verification during the lifecycle It is easy to get the two concepts mixed up	Point noted. Continued process verification has been amended to 'on-going process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
12	Please note that CPV (Stage 3, Continued Process Verification) in the FDA Guideline on general principles of Process Validation (January 2011) does not correspond to CPV (Continuous Process Verification) in this draft Guideline.	Point noted. Continued process verification has been amended to 'on-going process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
13	We are pleased to see the updated guidance, the alignment with ICH Q8, Q9 & Q10 and the inclusion of a lifecycle approach and Continuous Process Verification (CPV). We would advocate that the traditional approach to process validation be reserved exclusively for the revalidation of existing processes and not be used for new processes. The traditional validation approach tends to focus on meeting the final specification, rather than a full and proper understanding of the process and how the critical parameters affect the final result. From a perspective of statistical confidence, simply meeting specification on 3 consecutive batches is insufficient without a detailed understanding of the process mechanism and sufficient supportive data to demonstrate control and capability.	Point noted, however the proposal to keep traditional approach for revalidation purposes only cannot be adopted. It is still considered that both approaches are acceptable and can be used irrespective of the purpose of validation.

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	It is often said that one result meeting specification is chance, two are coincidence and three are validation! There is evidence to show that the pharmaceutical industry is some 30 years behind leading process industries in terms of the management of quality. Leading industries started a process of change towards total quality in the early 1980s. Today, industries including automotive, semiconductor, aerospace, consumer durables, etc. have embraced the cost/quality challenge and produce high quality products at minimal cost. To do this they use a wide range of tools, techniques and methodologies. There are few examples of these best practices being used in the pharmaceutical industry. Our experience of working in pharmaceutical manufacturing is that the industry can be very change-averse, and require significant encouragement to progress and apply modern approaches to process understanding and validation. Therefore we recommend that the guidance provides stronger recommendations relating to the application of continuous process verification and early process understanding through the development phase, and the application of appropriate analytical tools. The FDA has taken a more robust approach with the most recent Guidance for Industry on Process Validation and we recommend that the EU should take a similarly robust approach.	
14	The guideline gives more options to the manufacturer to ensure the validity of the product, which is welcomed. It	Comment not agreed. The activities leading to launch are GMP. This guideline focuses on the data to be provided in the dossier.

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	is somewhat abstruse; a clearer structure would be appreciated. A schedule of activities, including clearer relation of validation to launch, would be helpful.	
14	Differences between continuous verification (chapter 5.2) and continued verification (chapter 5.4) and annual product quality review are not clear.	Point noted: Continuous verification and continued verification are NOT to be confused with annual product quality review. Product quality review is a powerful GMP system that allows an overview of all quality performance and / or defects or trends. Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
14	It is unclear if the continued verification according to chapter 5.4 is necessary regardless of the type of process validation conducted (traditional or continuous).	Comment agreed – on-going verification can apply regardless of the type of process validation conducted. Continued process verification has been amended to 'on-going process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
15	The overall guidance does not appear to take into account the sampling plan to be used during process validation. National competent agencies (NCA) in various Member States have different approaches toward sampling plans. E.g. composite sampling is considered acceptable by some NCAs for conventional dosage forms, while it is deemed inadequate by others. In such cases, the commitment to conduct process validation with new sampling plan often delays the launch of the product. In this context, to introduce a harmonised sampling approach, we request QWP to consider sampling plan aspect as well in this guidance document.	Comment not agreed. Sampling plans are product specific and cannot be addressed in a guideline.
15	We believe that there are opportunities to explicitly	Comment not agreed. The stakeholder is referring to validation

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	mention the examples of tests to be conducted at various stages of manufacture. The tests to be carried out during start, middle and end of the production run during composite and/or multiple sampling should be mentioned as part of process validation. We recommend including these examples as a separate annex to the subject guideline.	protocols. The overall content of protocol is described in Annex 1 but more details cannot be developed in the guideline because the process validation protocol is considered product specific
15	The overall guidance should also encompass the qualification of facilities, utilities and equipments, which is very significant particularly for sterile preparations	Comment not agreed: The guidance is aimed at assessors. Qualification of utilities and equipment is part of EU GMP annex 15.
16	General comment when viewed in the context of the corresponding FDA Guidance for Industry document: • It would be beneficial for terminology to be aligned across the EMA and FDA documents. The basic requirement for and scope of Process Validation is effectively the same, however the two sets of guidance use different terminology to mean the same thing. • As these documents are likely to lead to further independently generated guidance for industry (eg ISPE), further harmonisation of terminology would be welcome. The EMA guidance is not directly relevant to API manufacture, whereas the FDA guidance is applicable to API manufacture.	Point noted. Efforts have been made to harmonise terminology between EU guidance and FDA guidance however due to differences in regional regulation (see above) it is not possible to harmonise further. On the other hand it is reminded that the guideline addresses data to be included in the dossier. Since validation data related to non-sterile API is not requested in the dossier the EMA guidance is not relevant for non-sterile API.
16	Other general observations: • Little emphasis on use of statistical expertise and tools, unlike FDA guidance which places much emphasis on this expectation. Science and risk based approach needed, but no specific guidance on	Point noted: statistics to be used should be proposed and justified by the applicant. No guidance on statistical tools will be given in the guideline. ICH Q9 is referenced in the guideline. This guideline should be read in

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	expectations. Little or no guidance on application of quality risk management, although it is expected.	conjunction with ICH Q8, 9 and 10.
17	EFPIA welcomes the opportunity to provide feedback on the draft "Guideline on Process Validation" (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). We think that the draft has certain merit but still needs significant work before it will be a coherent and effective guideline.	Point noted - no specific response required.
17	We welcome the overall intent to bring the guideline in line with ICH Q8, Q9 and Q10 principles. This provides opportunities for a more holistic approach to process validation across the product life-cycle. We note that the guideline states that "a lifecycle approach should be applied to process validation"; however we believe that the whole guidance should be structured around this concept. Ideally, it would be aligned with the ICH Quality Implementation Working Group Points to Consider, e.g. a three-stage approach of (1) Process Design, (2) Process Qualification and (3) Continued (or On-going) Process Verification. We believe that this would better realise the original intention of the concept paper on the revision to the Process Validation guideline (EMA/CHMP/CVMP/QWP/809114/2009), which implied that the revised QWP guideline would provide a more harmonised approach with the FDA guideline.	Comment not agreed. The definition used by the FDA in their revised process validation guideline cannot be adopted in the EU guidance due to regional regulation. Indeed validation guidance concern GMP inspectors at FDA level while validation guidance is aimed at assessors at EU level. Process design is already covered by ICH Q8. Duplication is not considered useful. This guideline should be read in conjunction with ICH Q8.
17	A science and risk based approach to process validation should be emphasized much more throughout the document. Systematic, science and risk-based approaches should be used to determine the scope and extent of process	Comment not agreed. The overall approach to continuous verification underlines that the verification should continue until the process is considered under control rather than predefine a number of batches for process verification. This is completely in contradiction with our understanding of continuous verification.

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	validation activities throughout the lifecycle of new products to ensure that the process will perform and continue to perform as intended. A risk based approach should be applied to define the number of batches for process verification. Based on process understanding and product knowledge less than three batches are acceptable to verify process performance. Also risk management tools should be applied to decide what a standard vs. non-standard method of manufacture is. We have considerable concerns about the distinction into standard and non-standard and in particular the broad definition of what is considered "a non-standard product or process". The use of such a distinction could stifle or discourage innovative approaches in pharmaceutical manufacturing, which is clearly not the intent. We think this Section 8 needs considerably more work before it is providing useful guidance. The distinction is very subjective and depends on an individual company's manufacturing capability and experience. Some processes listed as "non standard" are standard for some companies in view of their long experience and mastery with these processes used for numerous products. It is essential that companies can classify them as standard with a justification and provide data as necessary to demonstrate that the process is under control and product quality is met consistently. E.g., aseptic processing has been used successfully for decades and is not a novel approach to manufacture of parenteral medicinal products.	As regards the distinction between standard and non-standard processes it should be clarified that the concept does not apply when enhanced approach to development and continuous verification are applied. Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site.

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	Similarly, defining a specialised pharmaceutical dosage form can be subjective, as each dosage form will have its own unique considerations, e.g. emulsions and products with drugs in low content are well known and have been approved in Europe years ago.	
17	In general, it is welcomed that the guideline is practical in allowing the use of a conventional approach, a continuous process verification approach or a combination of both approaches. But we believe there are a number of aspects on Continuous Process Verification which are unclear and open to interpretation. In the guideline continuous process verification is related to "extensive in-line or at-line controls and monitor process performance in a timely manner." However, it is industry´s understanding and practice to regard also the life cycle approach with the three stages (Process Design and Development, Process Verification, On-going process verification) as continuous process verification approach. This section needs further development. It is not clear how Continuous Process Verification is positioned with respect to a traditional process validation approach – there are inconsistencies as to whether it is an alternative or an additional approach.	Comment not agreed. There is indeed a divergence in the understanding of continuous verification concept. Industry regard the lifecycle approach as the definitive of continuous verification whereas EU regulators consider continuous verification as an alternative to traditional process verification based on extensive on-line or at-line controls and monitoring of process performance. After internal discussion and a meeting with stakeholders in May 2013 the QWP decided to continue with the approach as defined in the guideline.
17	We do not see a need to limit the overall scope. We believe that the overall scope of the final guideline should apply to all drug substances and drug products, e.g. small molecules, biopharmaceuticals, vaccines and drug/device combinations. This would eliminate the need for several guidance documents on process	Point noted: The overall scope will only exclude active substances because for small molecules data is not requested in the dossier. It is worth noting that for large molecules a specific guidance is under development. The guideline applies for drug device combinations falling under directive 2001/83/EC.

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	validation which may potentially introduce different requirements. There is no reason why the same principles of a science and risk based approach would not be applied to these product categories.	
17	We have significant concerns about the guidance text related to validation across a Design Space at scale (see this section below). Pharmaceutical Companies are beginning to introduce innovative approaches to manufacture, e.g. continuous processing. It is essential that the final guideline should state that the general principles should apply to these innovative technologies in order to facilitate their application and implementation	Point noted: The term validation will be replaced by verification. A comprehensive new section clarifying the expectations behind design space verification has been included.
17	Consideration should be given to revising the EU GMP Annex 15 Qualification and Validation, to align the concepts and requirements and take the opportunity to harmonise terminology with the final EMA guideline	Comment agreed. Annex 15 is open for revision.
18	It is suggested that the title of the document be adjusted to more closely reflect its purpose. It is suggested that the "Guideline on Process Validation" be changed to "Guideline on Process Validation Information to be Included in Regulatory Submission" or similar.	Comment agreed. The title of the guideline has been updated.
18	It would be desirable to have additional information about statistical expectations in PV (if any) included in Annex 15 when revised	Point noted
18	When Annex 15 is revised, it would be desirable to have terminology harmonized with ICH and FDA PV Guidance, where possible. Explanation of any intended differences would also be helpful	Point noted

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18	It is suggested that the use of "continued" and "continuous" be clarified throughout the document: ISPE members are voicing concerns over mis-interpretation and recommend emphasising the differences. It may be helpful to create a separate section discussing implementation of advanced technologies for products already commercialized. It seems some of these are intermingled in other sections at present, which can be confusing. Using "advanced technology/PAT rather than "continuous verification" where appropriate may also improve clarity.	Point noted. Terminology will be revised. Continued process verification has been amended to on-going process verification. On-going process verification can apply regardless of the type of process validation conducted if advanced technologies are implemented. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
19	This document contains an extensive discussion on the use of continuous process verification in lieu of traditional process validation activities. This approach at the moment is still relatively unknown in the industry. Some clarification may benefit the majority of readers. The flow of information in this guideline is not optimal. It seems like elements of the new approach are being forced into the existing frame. Furthermore, the traditional approach seems to be considered at the same level as the new approach. This does not facilitate full realization of ICH Q8/Q9/Q10 and the formation of a new harmonized approach to process validation, where activities flow in a continuum. Additionally, it would be helpful to further illustrate how Continuous Process Verification would align with Continued Process Verification and to clarify whether these two approaches are mutually exclusive (see also under Specific comments, lines 290-294).	Point noted. Continued process verification has been amended to on-going process verification. Full realisation of ICH Q8-9-10 is not mandatory and the existing frame is still acceptable. Hence the guideline offers two options that are independent. Continuous process verification and on-going process verification are not mutually exclusive since continuous verification is an alternative to traditional process validation while on-going process verification ensures the state of control over the lifecycle. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
8-9	5	Comment: A clarification is proposed. Proposed change: This guideline replaces the Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99), including Annex II – Non-Standard Processes (CPMP/QWP/2054/03).	Comment Agreed Lines 8-9 have been updated to include Annex II.
31-33	17	Comment: The reference to "continuous process verification" from ICH Q8 provides the language that this is a "hybrid approach to process validation". We believe the guideline should stay consistent with the ICH definition (same as shown on lines 293-294) and use "alternative approach" rather than "in addition to, or instead of". Moreover, in other places in the document the two approaches are presented as quite separate, e.g. lines 138-139 and lines 175-176 – see further comments below. There is a need to ensure consistency. Proposed change: "...the possibility to use continuous process verification as an alternative approach to traditional process verification…"	Comment not accepted – the hybrid approach is a combination.
32-34	19	Comment: "… the possibility to use continuous process verification … has been added". Compared to the FDA guidance, where the use of modern concepts is encouraged, the approach seems to be more conservative. Proposed change (if any):	Comment agreed – The use of continuous process verification should be recommended where possible, but it is not possible to insist. Line 34 has been updated as proposed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"… the possibility to use continuous process verification … has been added *and is encouraged*". Even with this change, lines 34-37 are good enough to explain that "This guideline does not introduce new requirements …".	
32-34	13	Comment: The use of CPV should be a requirement for the validation of all new processes, not an option. Proposed change (if any): Make CPV a requirement for new processes, remove the reference to the traditional approach other than for the revalidation of established processes. proposed change to:- Lines 32, 33 and 34 '…with ICH Q8, Q9 and Q10 documents and the recommendation to use continuous process verification where ever practicable, in preference to the traditional process verification described in the previous guideline has been added…..'	Comment not agreed. The traditional approach is still considered a valid approach. Restriction of the use of the traditional approach to already authorised products may cause problems for smaller manufacturers who do not have the capacity to perform continuous process verification.
36	6	Comment: the word "*and*" in the sentence "…*coupled with risk management tools under and efficient*…" should be "*an*". Proposed change (if any): "…*coupled with risk management tools under an efficient*…"	Comment agreed. Typo on line 36 has been corrected as proposed.
39-43	19	Comment: The traditional definition of process validation is given and then it is added the "Continuous process verification has been introduced" but without a true definition. This leads to the possibility that the two approaches continue to co-exist and to lack of clarity on characteristics of the new approach. Proposed change (if any): We propose rewording of the	Comment not agreed. The two approaches can co-exist and definitions for both approaches are provided.

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		sentence: Delete "Process validation ….quality attributes" and replace by: "Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process."	
41	18	Delete "and quality attributes" since by definition a specification includes the quality attributes (Q6A and Q6B).	Comment not agreed – additional quality attributes may be present.
41-43	8	Comment: CPV can be used instead of Process Validation? It is not really clear, how this can be understood. Is it possible to omit process validation in case a strategy for CPV is in place? Proposed change (if any): Please clarify this sentence.	Point noted. Stakeholder should note that continuous process verification can be used instead of traditional process validation.
44-45	17	Comment: It is unclear how a CPV approach can be applicable where a traditional approach to pharmaceutical development has been taken. Lines 152-153 states that 'Sufficient knowledge and understanding of the process is required in order to support continuous process verification', which suggests that an enhanced approach, consistent with ICH Q8, must be taken.	Comment not agreed – continuous process verification can be introduced for legacy products where a traditional approach to pharmaceutical development has been taken, but sufficient knowledge has gained from manufacture.
44-46	17	Comment: This sentence is again in line 83-85, where it fits better than here. Proposed change (if any): Delete "CPV may be…performance."	Comment not agreed – sentence fits in both locations. Repetition is not considered to be problematic.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
45	8	Comment: "…traditional and enhanced approach to pharmaceutical development." This could maybe be specified a little more in details. Proposed change (if any): Please give examples, also for Biotech industry.	Comment not agreed – it would need to be addressed on a case by case basis by the applicant.
45-46	10	Comment: The document refers to "extensive in-line, on-line or at-line monitoring and / or controls to evaluate process performance" Proposed change: The terms in-line, on-line or at-line monitoring need to be defined.	Comment agreed – definitions have been added.
45-46	16	Comment: The document refers to "extensive in-line, on-line or at-line monitoring and / or controls to evaluate process performance" Proposed change: These terms (xx-line) need to be defined	Comment agreed – definitions have been added.
46	12	Comment: It is not clear what the difference between in-line, on-line and at-line is. Proposed change (if any): To include the above terms in the list of definitions	Comment agreed – definitions have been added.
56 and 171	17	Comment: These two lines appear to be in conflict with each other. Line 56 states that validation is not to be viewed as a one off event, while line 171 indicates that the applicant	Comment agreed – line 56 should stay as is, Line 171 has been updated.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		should indicate at which stage the product is considered validated. Proposed change: We suggest modifying the text in line 171 as follows: "At this stage the applicant should define when the process performance is verified and the point of commercialization of the product is achieved.	
56-58	9	Comment: This paragraph states, "*Process validation should not be viewed as a one-off event. A lifecycle approach should be applied 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*." While this can be considered an accurate statement we feel it is more helpful to describe the activities and principles on which process validation studies are based (rather than a statement of what PV is not.). Proposed change (if any): For clarity we recommend to: -Delete the first sentence of this paragraph, "~~Process validation should not be viewed as a one-off event.~~" -Revise the 2nd sentence to read, "Process validation incorporates a lifecycle approach ~~should be applied~~ 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."	Comment partially agreed – It is considered useful to retain the first statement to remind applicants of the lifecycle nature of process validation. The 2nd sentence has been reworded to state: "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.".
56-58	13	Comment: we support the use of a lifecycle approach.	Point noted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
60	18	Scope – We suggest modifying the scope to more clearly reflect the purpose of the document, ie., The intent of this document is to provide expectations for validation related information to be included in the registration dossier. This document should be utilized in conjunction with Annex 15, which explains compliance expectations associated with conducting PV.	Comment agreed. The scope has been updated.
60	18	Scope – Since 2003/63/EC directs that process validation studies shall be provided for active ingredients 'as appropriate', it is suggested that the scope reference ICH Q11 as containing the registration expectations for active ingredients and, therefore, this information is not repeated in this guide.	Point noted: Agree Principle applies – for further information refer to ICH Q11. – This is reflected in the scope.
60-62	8	Comment: "…to validate the manufacturing process of the intended commercial dosage form only. It is not directly relevant to the manufacture of the active substance or…." How can this be understood? Proposed change (if any): Please explain how to proceed in case of Drug Substance or Bulk Drug Substance production, especially for Biotech products.	Comment not agreed – QWP: This note for guidance is intended to apply to data submitted in the MA dossier. Only data generated to validate the manufacturing process of the intended commercial dosage form is requested in the dossier. For this reason, data generated to validate the active substance manufacturing process is not part of the scope. The general principles do apply however and the scope has been updated to include this. Biological drug substance and bulk drug substance are not within the scope of this guideline and will be dealt with in a separate guideline for process validation for the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			manufacture of biotechnology derived active substances.
60-68	6	The scope should state more clearly that the requirements provided in the guideline are applicable to new products and new production processes for existing marketed products.	Comment not agreed – This is covered under the variations regulation and does not need to be included in the guideline.
61	12	Comment: *"not directly"* is a weak wording. Please indicate that it could be relevant for DS by using a more active wording. Proposed change (if any): The sentence; *"It is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities."* is proposed deleted and replaced by: *"The principles outlined in this document may be applied to the manufacture of the active substance or other starting materials if deemed relevant"*.	Comment agreed – wording amended.
61-62	10	Comment: it is difficult to understand what is meant by: "It is not directly relevant to the manufacture of the active substance…" It is required to validate processes for active substances as well as processes for final drug products. What is the rationale for stating that the guideline is not directly relevant for active substances? Proposed change (if any): Please define the rationale.	Comment not agreed - This note for guidance is intended to apply to data submitted in the MA dossier; Only data generated to validate the manufacturing process of the intended commercial dosage form is requested in the dossier. For this reason, data generated to validate the active substance manufacturing process is not part of the scope. The general principles do apply however and the scope has been updated to include this.
63-65	20	Comment: the draft guideline states, "The fundamental principles described in this document are applicable to	Comment not agreed – see no need to specifically include small molecules.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		biological products, however, these should be considered on a case-by-case basis in view of…" As written, it may be unclear to the manufacturer that these principles are applicable to small molecules since it is not implicitly stated. Proposed change: to enhance consistency and utility of this guideline, the following revision is recommended: "The fundamental principles described in this document are applicable to small molecules and biological products, however, applicability to biological products ~~these~~ should be considered on a case-by-case basis in view of…"	
63-66	9	Comment: The Scope section includes the statement, *"The fundamental principles described in this document are applicable to biological products, however, these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance."* It is not clear how one should assess biological products on a case by case basis - what aspects of "complex nature and inherent variability" should be assessed? We have proposed some wording which leaves the guideline as applicable to biological products but recognizes the complexity of the biological substance. The words about 'case-by-case' and 'inherent variability' are not necessary and have been removed.	Point noted. *"The fundamental principles described in this document are applicable to biological medicinal products, however, these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance."*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): For clarity regarding the scope of the guideline, we propose revision of the above statement to read, "The fundamental principles described in this document are applicable to biological products, <u>but may require adaptation</u> ~~however, these should be considered on a case-by-case basis~~ in view of the ~~complex~~ nature ~~and inherent variability~~ of the biological substance."	
63-66	17	Comment: The scope of the guideline should include biologicals. The "complex nature and inherent variability" will be covered by using a risk-based approach. Proposed change: Delete "The fundamental principles... biological substance."	Not accepted. PDA suggestion followed,
70-72	5	Comment: A clarification is proposed. Proposed change: This guideline has to be read in conjunction with the introduction and general principles section (4) of Annex I to Directive 2001/83/EC as amended and the introduction and general principles section (2) of Annex I to Directive 2001/82/EC as amended.	Comment agreed: section 3 has been updated accordingly.
76	19	Comment: Examples of "exceptional" circumstances would add clarity for the reader. Proposed change (if any): Provide examples and guidance as to when concurrent validation may be acceptable.	Comment not agreed - Concurrent validation would be accepted on a case by case basis. This issue is covered under GMP.
76	8	Comment:	Comment not agreed - Concurrent validation

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		"…in exceptional circumstances concurrent validation may be accepted". Proposed change (if any): Please give some examples in which cases this approach is acceptable.	would be accepted on a case by case basis. This issue is covered under GMP.
76	10	Comment: The guideline should give more detailed advice on when concurrent validation may be accepted. Proposed change (if any): Concurrent release will be used rarely, but may be accepted for drugs that are medically necessary. In such cases distribution of batches to the market will be performed before complete execution of validation protocol steps, and based on an effective risk management approach to ensure quality of the drug throughout the drug lifecycle.	Comment not agreed - Concurrent validation would be accepted on a case by case basis. This issue is covered under GMP.
76	15	Comment: The guideline accepts concurrent validation in exceptional circumstances. It would be beneficial to discuss various approaches of process validation *viz*. concurrent, prospective, retrospective, along with the circumstances under which these approaches could be applied. Proposed change (if any):-	Comment not agreed - Concurrent validation would be accepted on a case by case basis. This issue is covered under GMP.
76-77	19	Comment: While for a traditional approach the sentence "Process validation should confirm that the control strategy is sufficient to support the process design and the quality of the product" is appropriate, it is too static in the case of the new	Comment not agreed – comment is valid for traditional and enhanced approach. Traditional approach can also be a dynamic approach.

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		enhanced approach, where that type of verification should be continuously performed. Proposed change (if any): Add wording relevant to the control strategy in the case of the new enhanced approach or – better – propose a harmonized vision of the control strategy, e.g. "…manufacturing processes should be designed and controlled to assure that the finished product meets predetermined quality requirements and do so consistently and reliably."	
77-79	20	Comment: The draft guideline states "The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. A matrix approach may be acceptable." It may be unclear to the manufacturer what a matrix approach is and how to appropriately utilize. Proposed change: To enhance consistency and utility of this guideline, it is recommended that the matrix approach term be incorporated into the Definitions section of the guideline and include an example as well (similar to High impact models). For example, "The matrix approach generally means a plan to conduct process validation on different strengths of the same product….a specific approach may include…"	Comment agreed – a definition for bracketing has been included. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
78-79	11	Comment: It is not clear if one could have matrix approach to site or strength or both	Comment partially agreed - Disagree regarding a bracketing approach to different

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. A matrix approach may be acceptable for a family of strengths for a product. If the same manufacturing process and controls including design space are being implemented at a subsequent site in an equipment train having the same design and operating principles then full validation at the subsequent site may not be required.	sites. Validation must cover all sites. However, a bracketing approach to different strengths could be acceptable. A definition has been included. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
79	15	Comment: It is stated in the general considerations that a matrix approach may be acceptable for process validation. However, little guidance is given on this subject. A paragraph describing key principles that can be considered in designing the matrix approach would be useful. Proposed change (if any): -	Comment agreed – A definition has been included. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
80	17	Comment: the text needs to make clear that a traditional approach to process validation can be adopted by a company even when an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained. The text should not suggest that in these 'enhanced' situations that continuous process verification is expected. Proposed change: Revise text to read "Process validation can be performed in a traditional way (as described below) no matter what approach to development has been taken:	Comment agreed – line 80 has been reworded to state: Process validation can be performed in a traditional way (as described below) regardless of the approach to development taken; however there is also the possibility to implement continuous process verification if an enhanced approach to development has been performed or where a substantial amount of product and process knowledge and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		however there is also the possibility to implement continuous process verification if an enhanced approach to development has been gained or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience."	understanding has been gained through historical data and manufacturing experience.
80-83	13	Comment: The application of continuous process verification should be encouraged, and therefore the guidance should be strengthened to show this is the preferred approach. Proposed change: `…however, it is recommended that, continuous process verification is applied when an enhanced approach to development has been employed….	Comment not agreed: the approach to development depends on the strategy of the applicant.
80-84	9	Comment: This sentence states, *"Process validation can be performed in a traditional way as described below; however there is also the possibility to implement continuous process verification if an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience*. A combination of process validation and continuous process verification may be employed." In addition to the above, we believe there may be a combination of approaches where the appropriate manufacturing technologies are available in the commercial manufacturing. Proposed Change (If any):	Point noted, however changes are not considered necessary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		We suggest additional language be added at the end of the last sentence and the paragraph should read, "Process validation can be performed in a traditional way as described below; however there is also the possibility to implement continuous process verification if an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience. A combination of process validation and continuous process verification may be employed where appropriate manufacturing technologies are available to enable this approach.	
83	21	Comment: Please clarify as to whether 'a combination of process validation and continuous process verification' can be employed for biological products.	There are no specific requirements for biologicals in this respect. The approach is equally applicable for biological products.
83-84	17	Comment: Typo in line - the word 'traditional' is missing. Proposed change: "A combination of traditional process validation and continuous process verification..."...	Comment agreed – The wording has been amended. Line 83 will state: A combination of traditional process validation and continuous process verification may be employed.
87	8	Comment: Proposed change (if any): - Please explain the expectations as to a feed-forward/ feedback control strategy? Could you please give examples? - Please define the limitations that would be acceptable to the Agency for a feedback control strategy for a controlled process. Would this entail a Proven Acceptable Range	Point noted. Examples not required. Feed forward, feedback loops should be self-explanatory.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		(PAR) from development studies? Could you please give examples?	
87	17	Comment: The introduction of feed-forward or feedback loops are not clearly linked to the topic of validation and the validation expectations for an adjustable process. It would be useful if the focus for validation of an adjustable process is placed upon verification / validation of the control system, since the process may change with every batch when an adjustable / adaptive process is used. Proposed change: Delete "When feed-forward... to maintain finished product quality."	Comment not agreed–continuous process verification is associated with the PAT approach of in-line monitoring etc. Continuous process verification should use continuous monitoring possibly using feedback loops.
87-88	11	Comment: Explain the type of feedback/feed forward being discussed. Also clarify on parametric control vs. attribute control Proposed change (if any): When feed-forward or feedback loops, for example, parametric and/or attribute based loops, are employed then it is possible to adjust the process during manufacture to maintain finished product quality.	Comment not agreed - the introduction of specific types of loops not considered necessary at this stage.
89	21	Comment: In addressing the term 'Process Validation', there can be a mention that PV equates to Process performance Qualification as defined in the 'FDA – guidance for process validation' to align with FDA guidelines.	Comment not agreed – the title of the guideline will change to more closely reflect the scope of the guideline.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
91	8	Comment: Does "all products" mean "all formulations"? Proposed change (if any): If so, please replace "all products" by "all formulations".	Comment not agreed – formulations can be addressed in the bracketing strategy..
91	6	Comment: "*Process validation data should be generated for all products….*": the possibility to validate a matrix of products should be clearly added. Proposed change (if any): "*Process validation data should be generated to cover all products (a matrix of products can be used)….*"	Comment not agreed. This is already stated under general considerations.
91 and subseq.	5	Comment: First paragraphs included in section 5.1. *"Traditional process validation"* are general and hence applicable to CPV as well. Their replacement to section 4. *"General Considerations"* is proposed.	Comment agreed – lines 91 – 95 have been moved up under general considerations.
91-95	17	Comment: The content of this paragraph is applicable also to the approaches describes in 5.1, 5.2 and 5.3. Proposed change: Move paragraph up and place after line 88.	Comment agreed - see above.
91 and 105	17	Comment: We see a mixed message since process validation is much more than just creating data. Also, the possibility to validate a matrix of products as mentioned in line 79 should be clearly added. Proposed change: "Process validation should be performed to cover all products (a matrix of products can be used)…" "…should be completed to cover each product (a matrix of products can be used)…"	Comment not agreed. This is already stated under general considerations. 'bracketing may be acceptable' has been added in line 106. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
92	21	Comment:	Point noted. In principle, data should be

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		If process validation data is not included in the submission – would it be asked to be provided during the review or a commitment to provide the relevant data prior to commercialization? Does this also apply to biotech/biologic products?	provided at the time of submission. If data are not requested in the dossier they should be available for inspection. Process validation data for biological medicinal products should be available at time of submission as generally the manufacturing process is considered non-standard. Only in very exceptional cases there might be a standard processes. In such cases the validation scheme has to be included in the dossier and validation data have to be available during inspection.
92-94	9	Comment: The 2nd & 3rd sentences of this paragraph read as follows, *"It is recognised that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilised."* The 3rd sentence is confusing, e.g., what is the definition of a "valid" manufacturing process if it is not validated? Our expert group had several different interpretations of the intended meaning of this sentence and could not agree on the intent. Proposed change (if any): Change the sentence in line 92-93 and add 'full/complete' before process validation to improve clarity. Then we recommend deletion of the sentence in lines 93-94 as it is confusing, and not really necessary in the context of the	Comment partially agreed – agree to delete sentence ~~'Nevertheless it is essential that valid manufacturing processes are always utilised'~~, but don't agreed to add full / complete."

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		remaining paragraph. The two sentences on lines 92-94, will then read, "It is recognised that, at the time of submission, full/complete process validation data may not always be available. ~~Nevertheless it is essential that valid manufacturing processes are always utilised~~."	
93-94	17	Comment: It is unclear what this requirement refers to. Surely, processes do not have to be validated during development and for clinical trial productions. Proposed change: Delete "Nevertheless... are always utilised."	Comment agreed – sentence has been deleted.
96-103	13	Comment: We are concerned that the inclusion of the value 10% will result in the assumption that this is a definitive number for validation based on pilot batches, not a minimum. Proposed change: Add, between line 95 and 96. '….The validation must include sufficient data to demonstrate that the process is statistically stable and capable and will consistently produce products meeting the defined attributes relating to identity, strength, quality, purity and potency and that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions.'	Comment not agreed – the concept of pilot scale being a minimum of 10% of production scale is already in use. It is clear from the text that it should be at least 10%.
97-103	8	Comment: 1.) Why factor 10% pilot scale to production scale? 2.) An example is given only for solid oral dosage forms.	Comment not agreed: The concept of pilot scale being a minimum of 10% of production scale is already in use for oral dosage forms.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): 1.) The scale factor should be significant and suitable for later scale up. 2.) Please also give examples for Biotech products and also for liquid dosage forms or lyophylisates.	For other dosage forms the pilot batch size should be justified taking into account risk to patient of failure of the dosage form. For biological medicinal products, pilot scale data are regarded as supportive can be used for development studies and stability; commercial scale process validation data should be available at time of submission (see also line 115 ff) For lyophilisation process validation runs might be performed with a justified mix of verum /placebo vials.
97-103	17	Comment: there is no reason to limit pilot batches to 10% of production scale. Proposed change: The scale factor should be significant and suitable for later scale up, based on risk assessment and future commercial batch sizes.	Comment not agreed - see above.
99	17	Comment: only an example for solid oral dosage forms is given. Proposed change: Add examples for other dosage forms, e.g. liquid dosage forms or lyophylisates, including biologicals.	Comment partially agreed - For other dosage forms the pilot batch size should be justified taking into account risk to patient of failure of the dosage form.
99-103	17	Comment: limitation of scaling, together with restriction that "... authority may decide on limitations for post-approval increase of batch size" could hinder process improvements such as significant scale increases or change to continuous processing. We assume this is not the intent, but that the	Comment agreed –'The competent authority may decide on limitations for a post approval increase of the batch size' to be deleted. For biologicals see above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		intent is to allow for limitations to be set on the initial commercial manufacturing scale. Proposed change: change text to read "In these circumstances, the competent authority may decide on limitations on the initial commercial manufacturing scale."	
100	21	Comment: In addressing the statement, 'For solid oral dosage forms this size should generally be 10% of the maximum production scale or 100,000 units whichever is the greater', please clarify if this rule is applicable to biological products.	See above.
100-103	17	Comment: These lines imply 100,000 unit batch sizes are the norm for solid dosage forms. This would have implications for products for rare diseases where batch sizes are typically <100,000 units. We believe that provision should be made for allowing lower batch sizes in certain circumstances, e.g. rare diseases.	Comment not agreed – a justification is allowed in the text.
102-103	5	Comment: as the proposed phrase is unclear we suggest deleting it or providing appropriate clarification regarding the cases/conditions where *"limitation for post approval increase of the batch size"* by competent authority could be possible. Proposed change:	Comment agreed –' The competent authority may decide on limitations for a post approval increase of the batch size' to be deleted
102-103	9	Comment: The last sentence of this section states, "*The competent authority may decide on limitations for a post approval increase of the batch size.*" The EU Guideline on the details of variations to the terms of marketing authorisations (currently under revision) defines conditions to be fulfilled and documentation to be supplied for any changes in the	Comment partially agreed –'The competent authority may decide on limitations for a post approval increase of the batch size' to be deleted - Additional text not to be added as it is clear variations regulations apply for changes.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		batch size of the drug product/ Proposed change (if any): Delete existing sentence in lines 102/103, and add new sentence as shown below. "~~The competent authority may decide on limitations for a post approval increase of the batch size.~~ As regards to any post approval changes to the batch size, reference is made to the respective EU Variations Regulation and related guidelines".	
105	6	Comment: "…*should be completed for each product*…": the possibility to validate a matrix of products should be clearly added. Proposed change (if any): "…*should be completed to cover each product (a matrix of products can be used)*…"	Comment agreed - add 'bracketing may be acceptable' in line 106. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
105 and 91	17	Comment: we see a mixed message since process validation is much more than just creating data. Also, the possibility to validate a matrix of products as mentioned in line 79 should be clearly added. Proposed change: "Process validation should be performed to cover all products (a matrix of products can be used)…" "…should be completed to cover each product (a matrix of products can be used)…"	Comment partially agreed - 'Bracketing may be acceptable' has been added to line 106. Bracketing has been included rather than matrixing as it was considered to be a more accurate description of the approach.
112	17	Comment: The basic principle of process validation should be stated more clearly. Proposed change**:** "Process validation should demonstrate the	Comment agreed: this is reflected under general considerations "Process validation should confirm that the control strategy is sufficient to support the process design and

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		ability of the defined control strategy to deliver the desired product quality."	the quality of the product".
112-113	18	A control strategy contains elements more than critical process parameters (definition ICH Q10) and therefore suggest "which primarily includes critical process parameters" is redundant and should be deleted	Point noted – comment is redundant as line 112 is being amended.
113	21	Comment: It would be helpful to provide some examples of "other relevant studies". Proposed Changes: Add the Abbreviation 'CPP' after "critical process parameters".	Point noted – comment is redundant as line 112 is being amended.
115	17	Comment: providing production scale validation data in the marketing authorisation dossier can mean that in those cases this production scale batches may be considered by some as not useable commercially. Proposed change: to avoid confusion, add that such production scale batches used in early validation may be commercialised after approval provided they are within shelf-life.	Comment not agreed – this is not the purpose of the guideline. This is considered to fall under GMP.
115-127	8	Comment: Does this mean that for biological / biotech products, pilot scale validation is not sufficient at the time of submission? Proposed change (if any): Please clarify.	*Yes, see above.*
115-127	9	Comment:	Comment partially agreed: This section has

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		These lines read: *"In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier, e.g. in those circumstances where the product is a biological / biotech product, where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale, or for specialised products such as certain modified release preparations (for medicinal products for human use, see the Note for guidance on quality of Modified release products; for those for veterinary use, see the Note for guidance on the Quality of Modified Release Dosage Forms for Veterinary Use). Where non-standard sterilisation methods or aseptic processing are employed, data should be provided on a number of consecutive batches at production scale prior to approval. The number of batches (minimum of 3) should be based on the variability of the process, the complexity of the process / product and the experience of the manufacturer. For other specialised non-standard processes (described in section 8), data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of products by essentially equivalent processes."* This section of the guideline is long, a bit confusing, and sometimes redundant, e.g. non-standard processes and the need for production scale data are also covered in in lines 237-244. Furthermore, some of the examples provided of 'non-standard methods' can become, over time, more common. Such definitions could change with time and	been reworded. Examples of processes have been deleted, but number of batches has been kept. Where non-standard processed are employed data should be provided on a number of consecutive batches. Batches must be consecutive to confirm process is capable of consistently producing a quality product.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		experience. We recommend the following deletions of text in this paragraph. The stipulation of the number of batches needed in some cases is inconsistent with the ICH principles and unnecessary. Proposed change (if any): We propose the following edits in this section: "~~In certain cases however,~~ It ~~is~~ may be ~~considered~~ necessary to provide production scale validation data in the marketing authorisation dossier. ~~e.g. in those circumstances where the product is a biological / biotech product, where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale, or for specialised products such as certain modified release preparations (for medicinal products for human use, see the Note for guidance on quality of Modified release products; for those for veterinary use, see the Note for guidance on the Quality of Modified Release Dosage Forms for Veterinary Use).~~ Where non-standard sterilisation methods or aseptic processing are employed, data should be provided ~~on~~ **from** a number of ~~consecutive~~ batches at production scale prior to approval. The number of batches ~~(minimum of 3)~~ should be based on the samples and the data needed to address **the** variability of the process, the complexity of the process / product and the experience of the manufacturer. ~~For other specialised non-standard processes (described in section 8), data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of~~	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		~~products by essentially equivalent processes."~~ With all shown changes made, the section would read: "It may be necessary to provide production scale validation data in the marketing authorisation dossier. Where non-standard sterilisation methods or aseptic processing are employed, data should be provided from a number of batches at production scale prior to approval. The number of batches should be based on the samples and the data needed to address the variability of the process, the complexity of the process / product and the experience of the manufacturer."	
115-117	17	Comment : At the start of this paragraph the text states that for non-standard methods of manufacture production scale validation data needs to be submitted in the marketing authorisation – this is reasonable but is made unreasonable when one reads what falls into the definition of 'non-standard' in Section 8 of the text. Proposed change: See comment on Section 8, line 234-236	Comment partially agreed – see comments on line 234-236
115-127	17	Comment: The paragraph that contains the requirement for a minimum of 3 batches should be made clearer. On first reading, it appears that a minimum of 3 batches for validation is expected. However, on careful reading of the whole paragraph it may just be referring to the data to be included in the MAA and the number of consecutive batches required at production scale for non-standard sterilisation methods or aseptic processes (the preceding sentence). At the end of this paragraph, it does state that for other	Comment partially agreed – this relates to data in the dossier (text has been amended to clarify requirements). Batches must be consecutive to confirm process is capable of consistently producing a quality product. Definition of consecutive is not considered necessary.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		specialised non-standard processes / products, data on 1 or 2 production batches may suffice when supported by pilot scale batches. Also, it is not clear why batches need to be consecutive and how "consecutive" is defined. Proposed change: This paragraph needs to be made clearer as to what the 3 batch number is referring to. This sentence could be mis-interpreted as currently written and positioned. Delete "consecutive" and emphasize risk-based approach.	
116	17	Comment: Biologic products are mentioned as an example of products that would require production scale data under traditional process validation. It is unclear why validation data for a biological product is required for initial submission. Biologics are a heterogeneous product family with a wide spectrum of properties. Significant progress has been made in recent years in the understanding and consistency of some of these products. Biologics drug products are often manufactured by relatively simple processes and would not necessarily fit with the definition of 'non-standard' needing upfront validation data to be provided. Proposed change: Replace "the product is a biological / biotech product" by "the properties of the active substance(s) of the products may give rise to processing, scale up or stability difficulties during manufacture at larger scale."	Aseptic processing usually applied in the manufacture of biological medicinal products is considered a non-standard process. Filtration, duration of filling, contact times etc. may impact on product quality (CQAs).
122-123	17	Comment: Sterile filter validation (Bacterial retention test) as part of the aseptic process validation is generally performed using an accepted scale-down model *(PDA Technical Report*	Comment not agreed – Bacterial Retention Test is addressing validation of filter properties rather than process validation itself.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		#26, "Sterilizing Filtration of Liquids," J.Pharm. Sci. and Technol. 52 (1 Supp) (1998)). The guideline should allow the application of scale-down models for validation of unit operations or aspects of unit operations where a conclusive justification can be provided, even for non-standard processes such as aseptic processing. Proposed change: Please rephrase according to comment.	
123	17	Comment: The text states the number of batches would be a minimum of three. It is unclear whether the number of 3 batches is applicable just to "non-standard sterilisation methods or aseptic processing" or to all processes described in this paragraph beginning at line 115. Establishing a minimum of three batches may not always be necessary, particularly in consideration of the ability to consider enhanced process knowledge. Based on risk analysis it should be acceptable that the number of validation batches is less than three consecutive batches on final scale. Later sections (line 172) require justification for number of batches, even if the number is three. It is unclear why for non-standard processes less than 3 lot validation is accepted when for standard processes more (i.e. three lots) have been traditionally expected. We think we read this as being the initial data to be provided in the MAA (not the full validation expectation), but this may be subject to mis-interpretation, due to the separation of the concepts in the text. Proposed change: **"**The number of batches (typically 3)	Comment partially agreed: – line172 refers to continuous process verification so it is not completely relevant to this section. The number of batches refers to the data to be submitted in the dossier. The total number of validation batches is a GMP issue. The stakeholder is incorrect when they state that the number of batches is less for non-standard processes. If 1-2 batches are accepted they must be supported by pilot scale batches and a history of consistent manufacture. For standard processes a PV scheme would suffice. Examples of processes to be deleted, but number of batches will be kept. Where non-standard processed are employed data should be provided on a number of consecutive batches See comment above. 3 is the minimum.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		should be based on the variability of the process, ... 1 or 2 production scale batches may suffice...” Clarify in this section whether the applicant must provide justification in case number of batches is 3. Clarify whether the number refers to data to be provided in the dossier or the total number of validation batches expected.	
123	17	Comment: The text as written does not seem to allow for the use of concurrent validation approaches. The text should be modified to allow for this approach to be used, when appropriate. Proposed change: Suggest text is changed to “Validation can employ either prospective or, when appropriate, concurrent approaches to validation. When employing prospective validation, the number of batches…”	Comment not agreed – This is considered to be a GMP issue - not within scope of this document.
123-125	22	Comment: The draft guideline specifies that minimum of 3 batches should be used for traditional process validation. The recommendation is that the guideline should not require a minimum number of batches for performing traditional process validation and the number of batches required should be determined using a science and risk-based approach. Proposed change (if any): The number of batches ~~(minimum of 3)~~ should be based on the variability of the process, the complexity of the process / product and the experience of the manufacturer.	Comment not agreed– number of batches should be based on science and risk, but it is unclear how this would lead to fewer than 3 batches.
123-125	11	Comment: Our understanding of the definition of traditional	Comment partially agreed: number of

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		process validation is that when PAT/RTRT is not employed for in-process control and releasing the batches. Even without the implementation of PAT/RTRT, if all the elements of QbD principles were used in developing the product and the process understanding then this information can be leveraged to reduce the number of batches and the firm should not be required to conduct a minimum of 3 batches for validation. Proposed change (if any): the minimum number of batches should be justified based on the variability of the process, the complexity of the process / product, process knowledge gained during development, supportive data at commercial scale during Tech transfer and the overall experience of the manufacturer.	batches should be based on science and risk, but it is unclear how this would lead to fewer than 3 batches. Proposed text to be adopted with the change highlighted below 'Data on a minimum of 3 production scale batches should be submitted unless otherwise justified'.
123-128	13	Comment: the inclusion of "minimum 3" will encourage the current flawed assumption that three batches in specification confirm the validated state. Proposed change (if any): include a statement that any validation must generate sufficient data to demonstrate that the process is statistically stable and capable. Add, between 127 and 128 "Where a product is manufactured using continuous processing technology, the rules apply regarding the provision of sufficient data to demonstrate the validity of the process, however the correspondence between the volume of data, its analysis methodology and critical processing attributes must be clearly justified and included within the process validation	Point noted –This section has been updated and the comment is now considered to be redundant.

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		scheme".	
127	8	Comment: Proposed change (if any): Please define "equivalent processes" in line 127 and the evidence required to support this declaration, i.e. comparability reports retrospectively?	Comment not agreed – this is to be justified by the applicant on a case by case basis. Examples will not be given in the guideline.
128	18	It is recommended that this sentence be either deleted or changed to be more easily understood and consistent with 2003/63 and ICH guidelines. It is not clear what 'those phases' are. Since contemporary use of the word 'phase' is usually in reference to a part of the lifecycle (Line 311), at least this word should be replaced by 'stages' or 'steps'. Is the intent to refer to 'phases (steps)' not controlled with the specification? A specification does not usually control a step, only provide assurance of the product quality (Q6A/B). We propose; "Where it is necessary to provide production scale validation data in the dossier, the validation studies should address those manufacturing steps deemed to be critical." It is not necessary to suggest 'by additional testing as necessary' since this implies that additional testing might not be required and then the only outcome is that the test data are captured in both the batch record and in a validation report	Comment not agreed – it is felt that this statement is useful to open possibility to have additional testing during validation. 'Phases' can be replaced by 'steps'
130-132	9	Comment: This sentence is a repeat of the text in lines 109-111 above, it reads, "*A justification for the chosen process validation studies should be presented in Module 3 and the Quality*	Comment agreed: sentence has been deleted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Overall Summary for human medicines, and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines." Proposed change (if any): Delete redundant text at 130-132, ~~"A justification for the chosen process validation studies should be presented in Module 3 and the Quality Overall Summary for human medicines, and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines."~~	
133	18	Suggest change from "if a design space is implemented" to "if a design space is to be proposed in the dossier". This is more consistent with purpose of the document – validation related information to be included in submission. Additionally, suggest a change from "should provide the validation strategy at production scale" to "should provide verification strategy to show the model is representative of full scale." We consider models to be subject to verification not validation. The guide does not indicate validation expectations when a proposed design space does not use a model (in the chemometric sense) or where a design space is based on dimensionless attributes. We suggest "Similarly, where a design space is proposed that does not use a statistical model, the applicant should provide a verification strategy to show that the design space is representative of full scale."	Comment partially agreed. Change from "if a design space is implemented" to "if a design space is to be proposed in the dossier" is not endorsed and will be replaced by 'if a design space has been developed'. In all cases, when a DS is implemented it has to be proposed in the initial submission or through variation regulation. The second part of the comment is agreed: Design space verification should be used rather than Design space validation. As regards "design space that does not use a model", the comment of the SH is unclear. Actually, any DS is derived from a DOE. It can be supported by a statistical algorithm (prediction model) or not. In both cases it should be verified at commercial scale. A comprehensive new section clarifying the

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			expectations behind design space verification has been included.
133-136	5	Comment: If a design space has been implemented, general recommendations regarding batch size and minimal number of batches needed for the validation purposes should be discussed in the guideline.	Comment not agreed - the verification of DS is process specific and should not be discussed in the guideline in terms of minimal number of batches. Applicant is invited to justify its strategy on a case by case. As regards batch size both validation and verification should be performed at commercial scale in the commercial equipment at the declared manufacturing site.
133-136	9	Comment: This section reads, *"If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. Validation at production scale may be conducted step-wise when the manufacturer moves to different areas of the design space."* It is unclear how this can be accomplished. The verification of design space presumably requires process parameters to be run outside of the normal operating ranges specified in the commercial batch records. Therefore, verification of design space established using qualified, scaled down models seems excessive at commercial scale. Conducting step-wise validation is confusing and inhibits design space development since more validation work may	Comment not agreed- actually the applicant is invited to submit its strategy and it is suggested that DS verification is not performed at the time of submission but rather stepwise depending on the product lifecycle and the business needs. The step wise approach is a relief from submitting data and does not inhibits any DS development. A comprehensive new section clarifying the expectations behind design space verification has been included.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		need to be interpreted than a traditional development approach. Proposed change (if any): suggest deleting sentence (line 135-136) With suggested changes these sentences should read, "If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. ~~Validation at production scale may be conducted step-wise when the manufacturer moves to different areas of the design space.~~"	
133-136	11	Comment: need to clarify what is meant by "Step-wise". It could be interpreted differently. Some clarification text is suggested. Need to include guidance on validation strategy if the design space is scale-independent. If the design space has been confirmed at pilot scale and verified at commercial scale during tech transfer, is there a need to validate again when moving into the different areas of the design space? Proposed change (if any): If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. If a design space has been proven to be scale-independent, then validation at production scale may not be required. Validation at production scale may need to be conducted step-wise when the manufacturer moves to different areas of the design space which has not been demonstrated to be	Point noted with following clarifications: - Step wise approach means that data can be generated later when the movement within DS is actually performed. It means that it depends on business needs. - It is not mandatory to verify DS at commercial scale at the time of tech transfer. However, If the DS is verified at time of tech transfer (means that the process has been verified in different areas of DS) then there is no need to verify the process again when it is deemed necessary to move into the different areas of DS. - When the DS has been proved to be scale independent, there is no need to verify the DS at scale. A comprehensive new section clarifying the expectations behind design space verification has been included.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		scale-independent.	
133-136	17	Comment: a Design Space may not only be defined at pilot scale but also based on small scale data. It is not clear why Design Space was placed under "5.1 Traditional PV". It would usually be associated with an enhanced approach. The guidance does not envisage e.g. the use of modelling and computer simulations (e.g. Monte Carlo techniques) as a way of supporting process validation: the emphasis still seems to be on generating data on from a number of commercial scale batches. This text crosses into the debate on design space verification and is potentially unclear and confusing. This paragraph of the text is of considerable concern and may inhibit Design Space development and utilisation. The sentence describing step-wise validation at production scale when the manufacturer moves to different parts of a design space is unclear (what does 'step-wise' mean here?). The description of this requirement is likely to inhibit the development of design spaces, since the requirements are potentially greater than if a company simply conducts a 'traditional' three batch validation, where there is no current expectation to conduct validation studies across all the proposed ranges for process parameters. This is due to the assurance provided by the control strategy, and the value of the control strategy remains in the verification of a design space. Thus, there should be no additional requirements related to step-wise validation or model validation provided the control strategy is appropriate. Furthermore, change to	Comment partially agreed : It is acknowledged that the DS verification should be in a separate section. It is also agreed that DS can be defined at lab scale. Step wise approach will be clarified (see previous comments). A comprehensive new section clarifying the expectations behind design space verification has been included. ~~However the debate on design space verification is rejected at this point~~. Relying on control strategy ignoring the effect of scale and equipment is not acceptable. It is reminded that the control strategy suitable at NOR may not be appropriate for all movements within DS and consequently the process may then benefit from an enhanced control strategy. This would typically fit into the principle of continued verification. The use of models and simulation (ie Monte Carlo simulations) can be envisaged provided that applicant unambiguously demonstrate and provide DS verification according to the protocol provided at the time of submission. A comprehensive new section clarifying the expectations behind design space verification has been included.

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		any process, with or without a Design Space, should follow standard change management principles and confirm the control strategy is appropriate. Proposed change: however, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by process design data. "Validation / verification of a design space (or changes within a design space) may be adequately addressed by application of the normal control strategy, without further requirements, if this is appropriately justified. The control strategy may include elements of real time release testing or parameter control that would support continuous process verification and hence 'concurrent' validation." In addition, additional text should be considered: "Design space verification should continue for future changes within the design space, managed within the company's quality system. " Alternatively, text could be added (simplified in lines 192) to "Subsequent to process validation and during commercial manufacture, companies should monitor product quality to ensure a state of control is maintained across the product lifecycle (including any movement within a design space." Add text to state 'Product manufactured using such a strategy remains marketable assuming compliance with the Design Space and given that it meets the specified quality	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		profile.' Design Space should have a chapter of its own. The use of models and simulations should be explicitly endorsed.	
134	19	Comment: Concern with requirement that design space be demonstrated at production scale. Proposed change (if any): Historically, design space and or proven acceptable ranges are defined during development. Demonstrating these parameters as part of validation would create deviations to approved batch documentation where processes are not run at the edge of the design space. Should provide flexibility as to when this is appropriate and clarify it is not the expectation to include these studies as part of the formal validation batches	Comment not agreed - stakeholder interpretation of this section is not accurate. It is not requested to demonstrate DS at commercial scale. It is rather requested to verify DS at commercial scale (see previous comments).
135	18	"Validation at production scale may be conducted step-wise..." We recommend to delete or revise this sentence. The extent of validation activity, if any, associated with movement within a design space should be commensurate with the science, risk and any control strategy modifications. Additionally, most design space movements would likely occur post-approval, which this guideline does not address.	Comment not agreed - actually the guideline acknowledges that DS movement would likely occur post approval. This is what is meant by "step wise" (see previous comments). A comprehensive new section clarifying the expectations behind design space verification has been included.
135-136	8	Comment: Does this mean that the whole design space needs to be verified/validated in full scale although a valid small scale model is available which justifies the design space?	See previous comments

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please clarify	
137	8	Comment: Proposed change (if any): The Guideline should describe more clearly if and how the Annual Product Review can be used as reference or base for Continuous Process Verification	Comment not agreed- Although Annual product review can support Continuous process verification, it is neither a reference nor a base for continuous process verification.
137	8	Comment: The Guideline should describe or guide through the minimum requirements for Continuous Process Verification. Proposed change (if any): Suggestion of topics to be evaluated: process parameters; raw material manufacturers; testing specification parameters, etc.	Comment not agreed - The proposed change is already described line 143 to 147
137	10	Comment: The guideline should give examples of products and processes which could be considered as standard, and provide better guidance to the applicant when continuous process verification should be the preferred strategy. Proposed change (if any):	Comment not agreed - Example of non-standard processes are addressed in Annex II. It is not intended to describe when continuous process verification is appropriate. It is up to the applicant to define and justify its preferred strategy.
137	17	Comment: the Guideline should describe more clearly if and how the Annual Product Review can be used as reference or base for Continued Process Verification.	Comment not agreed – annual product review and continued process verification are two different concepts. Annual review can be a tool used to gather data on continued process verification. It is well described in EU GMP and does not fall within the scope of this guideline.
137-182	13	Comment: we support this approach as it requires	Comment on traditional approach is not

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		manufacturers to understand their processes fully and properly. The traditional three-batch approach encourages the manufacturer to focus on the results, not how they occur and the factors that will have an effect on output quality. We are pleased to see reference to PAT. Proposed change (if any): Remove all references to the Traditional Approach other than for the revalidation of established processes.	agreed– traditional approach is an option and can still be used depending on the applicant's strategy.
138	17	Comment: this states that continuous process verification is an alternative approach to traditional process validation, which is not consistent with lines 32-33, which describes it as an alternative or an additional approach - there are other places where positioning of CPV vs. traditional approach is not clear. Proposed change: Please clarify.	Comment agreed – text to be clarified for consistency.
138-139 165-169	9	Comment: The current statements read, "Continuous Process Verification (CPV) is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8)." "A discussion on the appropriateness and feasibility of the CPV strategy should be included in the development section of the dossier and should be supported with data from at least lab or pilot scale batches. A description of the CPV strategy including the process parameters and material	Comment on confusion between continuous process verification and continued verification is noted. It is worth noting that continuous verification has been used in ICH Q8. To avoid confusion on-going process verification will replace continued process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		attributes that will be monitored as well as the analytical methods that will be employed should be included as described in Annex 1, with cross reference in the validation section of the dossier." The use of the terms "Continuous Process Verification" and "Continued Process Verification" can be confusing, especially where the CPV acronym is used. Their similarity makes it difficult to understand that the first term suggests an alternative approach to traditional PV, whereas the second term is applicable to all products and needs to be performed throughout the lifecycle. Proposed change (if any): In order to avoid confusion, PDA recommends that the terms be written out whenever they are used, and the acronym "CPV" not be used in the guideline. These statements would then read, "Continuous ~~P~~ process ~~V~~ verification ~~(CPV)~~ is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8)." "A discussion on the appropriateness and feasibility of the ~~CPV~~ continuous process verification strategy should be included in the development section of the dossier and should be supported with data from at least lab or pilot scale batches. A description of the ~~CPV~~ continuous process verification strategy including the process parameters and	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		material attributes that will be monitored as well as the analytical methods that will be employed should be included as described in Annex 1, with cross reference in the validation section of the dossier."	
139	17	Comment: The principles of QRM (ICH Q9) are integrated as part of process validation in the CPV approach and therefore should be referenced. Proposed change: "…(ICH Q8/Q9)…"	Comment not agreed - definition is an ICH Q8 definition and not an ICH Q9 definition.
140-144	17	Comment: CPV does not have to be real time or use PAT. Proposed change**:** "It is a science and risk-based approach to verify and …" "In order to... companies should monitor process performance and product quality in a timely manner."	Point noted. It is agreed that continuous process verification is not systematically RTR testing or PAT; However it is reminded that RTR testing and PAT fit perfectly with the continuous process verification strategy Proposed change not accepted
142-143, 147-151	19	Comment: "In order to enable continuous process verification, companies should perform, as relevant, extensive in-line or at-line controls" + "Process analytical technology applications … and multivariate statistical process control (MSPC) can be viewed as enablers for continuous process verification". While it is fair to say that Process analytical technology (PAT) is often associated to this approach, the amount of PAT used in commercial production should be defined as part of the Process Design phase when the initial Control Strategy is put together (in theory, it is also possible that at this stage it is	Comment not agreed - Expectations on PAT do not need to be developed further. It is up to the applicant to justify its approach to continuous verification and the amount of PAT used.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		decided that PAT is not needed during commercial production). Proposed change (if any): Describe expectations on the use of PAT in the Process Design phase and during commercial production.	
142-144	21	Comment: Clarification is required as to what 'timely manner' means – is it a defined periodic interval (i.e. 3/6 months) or is it more related to the # of batches manufactured (i.e. every 3-4 batches manufactured at the production scale)	Comment agreed – timely manner has been replaced by 'on each batch'
	9	Comment: The first sentence of this statement reads, *"Relevant process quality attributes of incoming materials or components, in-process material and finished products should be collected."* The term 'process quality attributes' is not an ICH or otherwise recognized definition in the industry. Deletion of the word 'process' will allow this sentence to read more clearly. Proposed change (if any): Change "process quality attributes" to "quality attributes," so the statement reads, "Relevant ~~process~~ quality attributes of incoming materials or components, in-process material and finished products should be collected*."*	Comment agreed – proposed change has been implemented.
144-146	17	Comment: "Process quality attribute" is not a definition used in ICH.	Comment agreed.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Relevant CQA's of incoming materials or components, in-process materials and finished products as well as pertinent process parameters should be defined and verified.	
147	21	Proposed Changes: Add the abbreviation 'CPP' to line 113 after the term 'Critical Process Parameter' and use only the abbreviation here.	Comment agreed.
147-151	17	Comment: the control strategy should depend on the nature of the product and manufacturing process. This sentence is very specific to solid dosage forms. Proposed change: delete this section, or, at least, consider limiting this to refer to the tools e.g. "Process analytical technology tools (including multivariate tools for data acquisition and analysis, process analysers, process control tools, continuous improvement and knowledge management tools) can be enablers for continuous process verification."	Comment not agreed - the sentence is just an example. The proposed change does not have any added value.
149	8	Comment: Sample size would be dependent upon the statistical analysis and claim for acceptable quality level (AQL). Does the Agency have an AQL in mind and is this throughout the batch at a predetermined time and or random times within the batch production cycle? Proposed change (if any): Please define the Agency's thought on "large sample size".	Point noted The approach to large sample size has been addressed at EU level by EDQM chapter 2.9. 47
156 and 160	18	Delete "and commercial experience", since this guideline is discussing the information to be submitted in the application prior to commercial sale.	Comment not agreed - previous site experience on similar processes can be taken into account.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			On the other hand since continuous verification can be introduced anytime during product lifecycle, the commercial experience is crucial and should also be considered.
162	23	Comment: '*The process should be verified on commercial scale batches prior to marketing*' appears to contradict the aims of CPV in as much that it implies a 'traditional validation' type approach at the start of commercial activities. Instead, apply additional monitoring as mentioned in point above. Proposed change (if any):	Point noted. The principle of verification on commercial scale batches applies to both traditional and continuous process verification approaches. However, the sentence has been deleted because it is redundant.
162	23	Comment: Provide clarity for the differences between verify and validate. Proposed change (if any):	Point noted: sentence has been deleted.
162	17	Comment: the expectations here are unclear. The implication is that at least two commercial scale batches must be manufactured to verify the process before CPV can be used for marketed product. This is apparently contradictory with the statement in line 176 – i.e. that CPV can allow commercial use of the first validation batch. If taking a continuous process verification approach, we believe that one production scale batch would be sufficient prior to marketing. If some of the confirmative study at commercial scale can be reported post approval as part of continuous process improvement, guidance on type of variation report would be helpful.	Comment not agreed. Line 162 is a general statement "The process should be verified on commercial scale batches prior to marketing" It does not undermine any number of batches nor it is contradictory with line 176. On the other hand line 176 does not give any indication about release of validation batches. As mentioned in earlier comments the guideline does not address GMP and release issues. These aspects will be handled during revision of annex 15.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The text indicates that processes validated by continuous process (CPV) verification should be "verified on commercial scale batches prior to marketing." The term verification is used to mean "validation" in line 33. Due to enhanced process design which allows for continuous monitoring and evaluation, the potential should exist for batches made in this way to be released concurrently. The use of concurrent validation is acknowledged in section 4 (line 76). Proposed change: Clarify expectations. Clarify that this statement applies to "verification" of the commercial scale (ie. ensuring that scale-up of the process performs as intended), and not process validation per se. Either way, the opportunity for concurrent release of batches should be described.	Sentence has been deleted.
162 and 170	18	Change "commercial" to "production" to be consistent with the rest of the guideline	Comment agreed.
162,171-172	5	Comment: It is stated *"the process should be verified on commercial scale batches prior to marketing"*. On the other hand Annex I anticipates that *"additional monitoring would be expected for the first commercial batches"* – likely to be part of the CPV (lines 365 and subseq.). It is hence proposed to provide in the guideline general recommendations on the minimum number of batches on which the applicant should define the stage at which the product is considered to be validated and allow for commercialisation in case of CPV. It seems that in some cases, e.g. when the process is well-characterized, understood and well-documented to have no scale	Comment not agreed - the number of batches to be included in a CPV protocol depends on process development, control strategy and history of the product at commercial scale. Hence it is up to the applicant to propose the adequate number of batches. This number will be assessed in view of the development data provided in the submission and overall control strategy.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		dependencies or when there are no critical equipment dependencies, even one commercial scale batch could be sufficient.	
163	18	Change to 'If a design space if proposed…..'	Comment noted. The sentence has been removed.
165	17	Comment: this sentence (and the later discussion in this paragraph – line 172-173 on number of batches) – assumes that CPV will be used with batch processes. Continuous processes should be considered in the discussion of CPV. Proposed change: Revise section 5.2 (and 5.3) to include consideration of the validation of continuous processes.	Comment agreed. It is acknowledged that continuous process verification is most appropriate for validation of continuous processes. Section 5.2 has been revised accordingly.
165-166	17	Comment: This text seems to introduce new registration requirements. It may be reasonable to provide a rationale / justification for a CPV approach but it is not clear why data need be provided from this approach in the initial application (when such data might not be needed for the same product if a 'traditional approach' to validation was taken). Proposed change: remove the need to provide such data in the MAA	Comment not agreed. Data from pilot batches is requested to demonstrate adequacy of continuous process verification approach to the product and process.
169-171	9	Comment: The guideline reads, "*Actual data generated during continuous process verification at commercial scale should be held at the site for inspection*." From a GMP compliance perspective, regulators have long permitted archiving of data off-site and/or at centralised locations and not "held" at the site. The expectation is that	Comment agreed – proposed change accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		the relevant data can be made available for inspection at the site of the inspection when requested. Proposed change (if any): Change the word 'held' to 'available' to read, "Actual data generated during continuous process verification at commercial scale should be ~~held~~ available at the site for inspection."	
171 and 56	17	Comment: these two lines appear to be in conflict with each other. Line 56 states that validation is not to be viewed as a one off event, while line 171 indicates that the applicant should indicate at which stage the product is considered validated. Proposed change: we suggest modifying the text in line 171 as follows: "At this stage the applicant should define when the process performance is verified and the point of commercialization of the product is achieved.	Comment agreed. This section has been amended to 'The applicant should define the stage at which the process is considered to be under control and the validation exercise completed prior to release of the product to the market, and the basis on which that decision will be made'
171-172	8	Comment: Is the applicant expected to retrospectively or prospectively define the point of validation with CPV? Is this anticipated in a master plan or protocol for CPV or in a final report for validation? (One could say the claim of validation for the process being monitored is identified retrospectively while done prospectively.) Proposed change (if any): Please clarify the applicant's documented path for defining	Comment agreed. In principle applicant is expected to define the point of validation prospectively. However this does not preclude changes to initial scheme such as retrospective extension or reduction of the number of batches to be included in the scheme. Since the schemes are appended in the regulatory section, any change to the scheme should be handled through appropriate

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		validation claims when using CPV. Would this defined path be documented/referenced in Module 3's Overall Quality Summary?	variation regulation.
171-174	9	Comment: The sentences read, *"The applicant should define the stage at which the product is considered to be validated and the basis on which that decision was made. The discussion should include a justification for the number of batches used based on the complexity and expected variability of the process and existing manufacturing experience of the company."* Proposed change (if any): Consistent with the concept of PV over the product lifecycle, we suggest modifying the sentences to read: "The applicant should define the stage at which the product is considered to be ~~validated~~ under control and available for commercial distribution, and the basis on which that decision was made. The discussion should include a justification for the number of batches used based on the complexity and expected variability of the process and existing manufacturing experience of the company."	Comment agreed. Proposed change from EFPIA accepted with slight amendment.
172	17	Comment**: i**t seems unnecessary to justify the number of batches to be used when using continuous process verification. Provided the continuous process verification approach has been adequately designed to assure the performance of the process and the quality of the product then it should be capable of showing the quality of a single batch or multiple batches. Thus there should be no need to	Comment not agreed - the number of batches should be specified as part of the continuous process verification scheme.

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		justify a number of batches as CPV can support product quality in an ongoing and continuous manner. Proposed change: recommend this sentence is omitted.	
172-173	18	Change 'was' to 'will be' and 'used' to 'to be used' since the decision occurs in the future	Comment agreed. Section has been updated
175-178	17	Comment: we would like to request clarity on how to manage CPV introduction in commercial manufacturing. Proposed change: suggest adding: "Continuous process verification can be introduced in commercial manufacturing for already marketed products following the company's internal change management procedure (ICH Q10). In case regulatory relevant changes are made, a variation procedure according to Regulation (EC) No 1234/2008 shall be initiated."	Comment not agreed - it is unclear how continuous process verification introduction in commercial manufacturing can be made without any regulatory implication. continuous process verification is an overall strategy for process verification. As such it should be introduced through EU variation regulation
	17	Comment: this sentence could indicate that CPV can support process validation, which is different from saying that CPV is an alternative approach to process validation (as per line 31-34) - the same sort of confusion exists in lines 184-185, where CPV is seen as an alternative to traditional process validation. Proposed change: please clarify.	Comment agreed. Continuous process verification is an alternative to process validation. Line 175-178 should read "it can be used for the initial commercial production, to re-validate commercialised products as part of process changes or to support continual improvement"
179	18	Delete the whole paragraph. It is not clear how one measures CPV performance. Additionally, the totality of product quality depends on compliance with GMP principles, not just CPV, and so this section is redundant.	Comment partially agreed ; It is acknowledged that the totality of product performance depends on compliance with GMP principles. However, as far as continuous process verification is concerned it is worth

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			indicating that even if Continuous process verification strategy is adequate, it cannot achieve its goal if it is not supported by strong GMP systems. Hence the section will not be deleted.
179	17	Comment: we think that the word 'performance' here is confusing. Proposed change: change to "Continuous process verification is dependent on compliance..."	Comment agreed.
179-182	13	Comment: The importance of good basic GMP on the ability to obtain meaningful data from the application of continuous process verification will benefit from additional emphasis. Proposed change: Line 180, add "….requirements. Manufacturers applying continuous process verification must take into account their application of basic GMP principles and ensure they are complaint to a high standard	Point noted. The proposed change does not introduce any added value. It will not be implemented.
180	17	Comment: "Pharmaceutical quality systems (PQS)... as appropriate." This is not specific to CPV and can be applied to the traditional approach as well. Proposed change**:** Move these two sentences to a separate section.	Point noted. It is true that PQS apply to both traditional and enhanced approach. However, these sentences have been introduced in this section to address confusion between PQS such as handling of deviations and Product annual review with the principle of continued process verification.
183-190	13	Comment: We do not support the use of a hybrid approach other than	Comment not agreed - since both traditional and continuous process verificationapproaches

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		where there is a mix of process steps, some of which are established and have been validated previously using the traditional approach. Proposed change (if any): in line 185, add the comment: Where the process consists of one or more process steps that have been validated previously using the traditional approach, they may, by exception, be revalidated using the traditional approach. Any new or significantly changed process steps should be validated using CPV.	are acceptable there is no reason why hybrid approach would not be used for new processes.
184	18	Reword this sentence to be consistent with the scope of the guideline applying to the information to be submitted in the application. E.g., "The applicant may choose to use either…. It should be clear which approach to validation will be taken….the number of batches will depend upon…..."	Comment not agreed. The section does not show any contradiction with the scope of the guideline.
186	17	Comment: this text introduces additional registration requirements. Why should it be necessary to justify a hybrid approach to validation – this should be an accepted approach that should need no specific justification. Proposed change: remove this text.	Comment partially agreed. It is acknowledged that justification for using the hybrid approach is not necessary. However it should be clarified in the dossier which approach applies to which unit operation. The text has not been removed but rather changed to remove need for justification.
189	18	Delete the sentence. We believe that CPV can provide an equivalent, or even higher, assurance of quality for both standard and non-standard processes and thus all three options should be available to the applicant. Section 8 line 229 does suggest the acceptability of CPV for non-standard processes. If this recommendation is accepted, the sentence	Comment agreed. The sentence at line 189 can be changed to read "For non-standard processes (as defined in section 8) if continuous process verification does not address the critical unit operation(s) the process validation requirements

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		at line 255 can also be deleted.	highlighted in section 5.1 should be applied unless otherwise justified". Line 229 will not be deleted since it clarifies to the reader that the principle of standard and non-standard are not applicable when continuous process verification is implemented.
189	17	Comment: our interpretation of this statement is that for non-standard process, only a traditional process validation approach may be taken. It is not clear why a CPV approach may not be taken. Further clarification is needed.	Point noted. Please see previous arguments.
191	18	We suggest that 5.4 be made into a stand-alone section (eg, Section 6) to help reduce ambiguity. As a subsection of 5, it could appear that continued process verification is an option in the same way as the hybrid approach or continuous verification. In fact we believe that continued process verification is not optional and the guide should make it clear that it is an expectation irrespective of the approach used	Comment agreed Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
191	12	Comment: As section 5.4 (Continued Process Verification during the lifecycle) is included in section 5 (Process Validation), it is not clear if Continued Process Verification cover both traditional process validation and continuous process verification. Proposed change (if any): Consider to Change Section 5.4 to Section 6 since it is a process performed subsequent to Process Validation, Section 5.	Comment agreed - see previous outcome from ISPE.
191	15	Comment: there would be value in further elaborating the	Point noted

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		key principles of validation lifecycle for continued process verification (section 5.4). There is a scope of improvement in further structuring the presentation and content of section 5.4, in order to provide more clarity on the subject. Proposed change (if any): -	
191-205	19	Comment: The section about "Continued Process Verification" is high level in order to be linkable to both the traditional and the enhanced process. For this reason, it is not well defined in what it differs from the existing Annual Product Quality Reviews. Proposed change (if any): Better integrate this step with previous steps.	Comment not agreed. Stakeholder states that continued verification is mandatory whatever the approach to validation is. It is obvious that there is confusion between PQS requirement 'annual review and handling of deviations, complaints, and the principle of continued verification. Whereas PQS is mandatory, continued process verification is considered part of the enhanced control strategy.
191-205	13	Comment: this section focuses on the quality of the output, rather than encouraging a full and proper understanding of the process drivers (inputs and process parameters) that affect the quality of the output. We recommend that the section is clarified and strengthened to highlight the importance of all inputs & process parameters, as well as incoming materials, components, in process and finished product results. Proposed change (if any): Clarify that the process must be understood in sufficient detail and depth to generate a level of confidence that the critical parameters (inputs and process) are in control and capable throughout the product lifecycle.	Comment not agreed - the importance of input and process parameters is considered part of process development. At this stage, unless criticality has not been adequately addressed, the continued process verification is aimed at confirming that the process is under control and enhancing process understanding.

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194	17	Comment: The term 'capability' of a process has meaning beyond that intended in this sentence. We believe its use here could lead to confusion. Proposed change: Simplify this text to avoid this complicating double meaning – e.g. "This will provide assurance of the continued ability of the process and controls…"	Comment agreed.
196-199	17	Comment: Statement starts with "Relevant process trends" but all of the examples provided are more in line with quality trends. We also suggest adding the aspect of variability. This section relates very closely to Periodic Product Review/Periodic Quality Reviews. It could be helpful to provide guidance recognising the link between CPV and Periodic Quality Reviews as described in Q10 Section 3.2.4 (a) (2) (ii). Proposed change: "Relevant process and quality trends and variability, e.g. critical process parameters as well as quality of incoming…" Add the following sentence in line 199 after "…control strategy". "The outputs of this monitoring can be utilised in Periodic Quality Reviews (ICH Q10) of products for human use. A lower level of monitoring may be appropriate for established processes with a history of consistently achieving the pre-defined quality characteristics."	Comment agreed. Proposed change is accepted. However this stage is typically the stage where the process capability should be established. This point will be captured in this section. Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
199	14	Comment: ongoing process validation, should it be continued process validation?	Point noted. 'On-going' has replaced 'continued'.

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		Proposed change (if any): The extent and frequency of continued process validation should be reviewed....	
199-201	17	Comment: Any ongoing process validation would be in response to process or equipment changes, or to observed trends. However, the degree of process monitoring and testing may be adjusted based on the level of process understanding. The wording should be revised to clearly distinguish ongoing process monitoring from ongoing process validation. Any revalidation activities should be based on signals or changes, and should not be performed based solely on passage of time. Propose that where continuous process verification is used and reviewed in real time, that periodic continued process verification requirements may be limited (e.g. to a review of product defects reports for incoming raw materials and components, and non-conformances during in process and release testing.) Proposed change: the extent and frequency of ongoing process monitoring and testing should be reviewed periodically and modified if appropriate throughout the product lifecycle considering the level of process understanding and process performance at any point in time, and in response to planned changes.	Comment not agreed- PQS and Continued Process verification should not be confused. See previous comments. Stakeholder is reminded that continued process verification should not be restricted to planned changes.
199-204	12	Comment: Is "on-going process validation" as mentioned in line 199 and "continued process verification during the lifecycle" in line 204 the same?	Comment agreed. Continued process verification has been amended to 'on-going process verification. To avoid confusion between both terms they have been spelled in full and acronyms have been

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	avoided. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
201	18	Continued process verification should entail enhanced sampling and monitoring, dependent upon process variability, otherwise there is no difference from the normal (registered) control strategy. We recommend that the sentence be amended to "Hence, according to the performance and variability of the process, defined periods of enhanced sampling and monitoring should be established to provide increased process understanding as part of continual improvement."	Comment agreed - Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
201-203	17	Comment: It needs to be made clear that if sufficient process understanding exists prior to commercialisation, increased sampling post commercialisation may not be required.	Comment not agreed - the comment is in contradiction with the principle of continued process verification where it is requested to implement enhanced controls, as appropriate, during product lifecycle. Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
203	18	Change "continuous" to "continual" (Q10).	Comment agreed. Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
203	18	Insert a comma "If high impact models are used, as part"	Comment agreed Continued process

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		since the models are not themselves used as part of the process verification.	verification has been amended to 'on-going process verification.. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.
203-205	11	Comment: we assume that there will be a need to submit a variation if the high impact models were developed post approval for continued process verification. Which category of the post-approval variation would be applicable in this case?	Comment noted - it is not part of the scope of this guideline to define the type of post approval variation requested to introduce high impact models.
205 and subs	17	Comment: requirements and approach for existing products should be clarified. Proposed change: **i**nsert "Manufacturers of existing products can take advantage of the knowledge gained from the original process development and qualification work as well as manufacturing experience to continually improve their processes. Implementation of the recommendations in this guidance for existing products and processes would likely begin with the activities described in this chapter."	Comment not understood.
206-216	17	Comment: taking into account the increased level of understanding associated with a continuous verification approach, we would like to propose to allow applicants/marketing authorisation holders to validate their process at partial scale (for instance 20 % if this represents already a significant industrial size) at the time of the submission of their MA / variation application and to provide 100 % scale validation data before marketing of the product	Comment not agreed. There is a misunderstanding of regulatory expectations : In case continuous process verification is implemented data at production scale is not requested. What is requested is data at pilot scale.

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		as a commitment.	
207	17	Comment: this paragraph addresses the use of development data to justify that scale-up can be achieved without compromising quality, but is unclear about what is seen as compulsory information under which circumstances. For example, it introduces a definitive requirement to identify in P.2 and P.3 steps critical to scale-up, which is described as optional (for P.2) in ICH Q8 and has thus far been understood as being associated with an enhanced (QbD) development, but not necessarily with a traditional approach. When any intended manufacturing scale is adequately supported by validation data prior to commercialisation, current requirements do not demand a level of process knowledge facilitating definitive identification of the criticality of each step in relation to scale-up. Proposed change: It should be clarified that the requirement to identify steps critical for scale-up is limited to situations where it is intended not to perform appropriate validation studies to confirm quality at a given scale. Suggesting changing to: "Where feasible and scientifically and technically justified, it may be possible to utilise information from laboratory or pilot scale when scaling up from laboratory through pilot to production scale."	Comment not agreed – this is not a new requirement.
207-216	17	Comment: this scale-up section is useful and does suggest that scale-up within a well-founded Design Space supported by a well founded control strategy should be possible without significant re-validation or verification. We assume this section applies to biologics and non-standard	Comment not agreed. this section does not refer to design space. Design space scale-up is addressed in the design space verification section.

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		processes. Clarification in this regard would be appreciated. In addition, it is noted that revalidation may not be required when the process has been proven to be scale independent or also when the control strategy is scale independent. Proposed change: add text to note that "Scale-up within a well-founded Design Space support by a well -founded control strategy should be possible without significant re-validation or verification." Add a sentence explaining whether it is possible to justify scale independence for biologicals and non-standard processes. In addition to the previous suggested change to this section, please also amend text to read "It is envisaged that those parameters listed in the process validation scheme (Annex 1 of this guideline) will need to be re-validated once further scale-up is proposed unless the process or control strategy has been proven to be scale independent."	Verification of a design space after scale-up should be performed for biological medicinal product in any case. It is always expected that a design space and the control strategy is well founded.
211	17	Comment: suggest avoiding 'critical' as this is a result of a QRM process. Proposed change: "… to be dependent on scale-up".	Comment not agreed. The use of 'critical' is considered appropriate in this context.
213	17	Comment: the scope of this paragraph is unclear – applicability only to instances where no validation data are presented in the dossier, only a validation scheme? Proposed change: the paragraph may benefit from being split into two. A first section could give expanded advice on what is	Comment partially agreed – line 213 has been amended to state 'it should be justified…' , but further examples will not be given.

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		expected in support of a range of batch sizes under both sets of circumstances - when validation data are presented in the dossier vs. when not – e.g. the role of development data showing a process to be scale independent, possibilities for matrixing in traditional validation…… The last sentence addressing future scale changes should be edited to be applicable to both sets of circumstances - when validation data are presented in the dossier vs. when only a validation scheme is submitted. Editorial change: with the exception of process steps which have proven to be scale-independent.	
213-214	12	Comment: As the text is written now it is required that for the range of batch sizes it should be shown that the variations do not alter the characteristics of the DP, which means that studies might be required to demonstrate no changes in the characteristics properties. Proposed change (if any): To change the word *"shown"* to *"justified"* and to change the word *"characteristics"* to *"CQAs":* *"Where ranges of batch sizes are proposed, it should be ~~shown~~* justified *that variations in batch size would not adversely alter the ~~characteristics~~* CQAs *of the finished product.* "	Comment agreed – line 213 has been amended to state 'it should be justified' and change to CQAs agreed.
217	17	Comment: we suggest a rewording for consistency reasons. Proposed change: "Post approval change management"	Comment not agreed
220	17	Comment: it is unclear what 'tightly' adds to this sentence.	Comment agreed

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		Proposed change: Remove word 'tightly' from this sentence	
222	17	Proposed change: change 'specification' to 'control strategy'	Comment agreed
228	8	Comment: How can standard vs. non-standard be understood for biotech and biological processes? Proposed change (if any): Please give examples	Standards vs. non-standard processes refers to different manufacturing processes independently whether the active substance is a biologic or not.
228	17	Comment: this section describes a number of manufacturing methods that may be considered as "non-standard". Though the list may have had merit years ago, many of the cited examples are now common processes supported by a history of successful manufacture. Some examples include lyophilization, suspensions, modified release, and aseptic processing. Standard methods of manufacture are not discussed. In addition, this section is considered to be unclear with respect to standard and non-standard methods of manufacture. It should not be based on a general selection of what could be considered non-standard. The guidance provided is subjective and could be open to mis-interpretation. The same applies to terms "conventional processes", "specialised". This subjective nomenclature adds no clarity. Proposed change: the list of processes that may be considered as "non-standard" should be revised to only include those that are not in common use. Greater emphasis	Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.

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		should be focused on the manufacturer's demonstrated capability than on the nature of the process. Evaluate if a statement like this is more appropriate/helpful – "The need to manufacture scale-up lots should be commensurate with the manufacturing process risks and applicant's knowledge of the process."	
229	17	Comment: the tense should indicate that this section needs to be evaluated prior to completion of process validation. Proposed change: this section is only relevant for processes which will not be validated using continuous process verification (see sections 5.1 and 5.2).	Comment agreed
233-236	5	Comment: deleting of this phrase is proposed as a systematic list of non-standard processes are included in the draft guideline below. Proposed change:	Point noted: section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
233-236	12	Comment: Comma to be deleted. Proposed change (if any): Non-standard methods of manufacture could include non-standard methods of sterilisation and, aseptic processing, or processes with critical steps such as lyophilisation, micro-encapsulation, certain mixing, coating processes and other specialised processes.	Point noted, however this section has been revised, and it is not applicable anymore.
237-239	18	The Guide states, "The following categories are examples of	Comment agreed: agree on the principle of

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		products or processes which could be considered as non-standard, and for which production scale validation data might need to be provided in the marketing authorisation application dossier, unless otherwise justified:..." Suggest adding another sentence suggesting some basis by which applicants could justify that a process is standard for them, such as, "An applicant could potentially justify that a process is standard, based on experience with similar processes, products, number of batches manufactured with a similar process, similar process capability analysis, excipient and control strategy risk assessments, etc."	the comment. Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
237-239	5	Comment: an change is proposed as for some of enumerated non-standard processes, validation data needed to be provided in the marketing authorisation application dossier not necessarily have to come from production scale batches only (see lines 125-127). Proposed change: The following categories are examples of products or processes which could be considered as non-standard, unless otherwise justified.	Comment not agreed – some level of production scale data are required in the dossier for non-standard products and processes. Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
238	17	Comment: This states that 'production scale validation data might need to be provided'. Clarification is required as to what the expectations are.	Point noted: – Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process. Annex II updated to state 'production scale data should

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			be provided'.
245	17	Comment: The text states that "a manufacturing process type not previously approved for pharmaceutical products within the EU is usually considered a non-standard dosage form". This raised two concerns – (1) if a particular process has been registered by one applicant and others have no experience of this process type then perhaps this process should still be a non-standard process for other applicants. (2) How will an applicant know if a process has been registered previously and is considered to be simple and hence not requiring consideration as a non-standard dosage form? Proposed change: Please consider how to give clearer guidance on these points.	Point noted: Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
252	17	Comment: as per statement in line 34, it should be clarified that this is not expected for existing products. Proposal: Add 'for new submissions'.	Comment not agreed – this may be required for certain types of variations.
255	17	Comment: only section 5.1 on traditional validation is mentioned where data is to be included but sections 5.2 and 5.3 are on CPV and hybrid approaches and applicable. Proposed change: Change to "are detailed in sections 5.1 – 5.3".	Comment not agreed – this section is not relevant for continuous process verification as stated in the text, and regarding hybrids the requirements are as per 5.1.
261	8	Comment: The wording is ambiguous with regard to suspensions and emulsions. Does it mean only suspensions and emulsions for	Comment partially agreed. Section has been revised.

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		parenteral use? Please clarify. Proposed change (if any): • "Suspension, emulsions or liquid dispersed Parenterals"	
262	17	Comment: we do not believe all modified release (MR) preparations should be considered as non-standard products. Certain types of modified release products are well-precedented and simple to manufacture (e..g monolithic matrix MR tables). Proposed change: please reconsider that all MR products should be non-standard. Either include more specific mention of MR product types that would be considered non-standard or provide some MR product types that can be considered as standard products.	Point noted: section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
263	23	Comment: '*Unit dose products containing drugs in low content (<= 2% of composition)*' – please clarify whether that is a total of all component drug content or any single component for products which have multiple APIs. Proposed change (if any):	Any single component for products which have multiple APIs.
263	17	Comment: when assessing unit dose products containing drugs in a low content (≤2% of composition) the corresponding manufacturing process should be taken into account as well (e.g., direct compression versus spray granulation). Proposed change: consider rewording as suggested above.	Point noted: section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
268	23	Comment:	Comment agreed –The wording has been

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		'*introduction of a new technology*' – please clarify whether this would be new to the industry or new to the firm. Introduction of an established technology that is new to a firm may present significant risk. Proposed change (if any):	amended to put more emphasis on experience of manufacturer to take into account of this.
270	23	Comment: '*full-scale validation*' – please clarify what is meant – assume that reduced approaches such as bracketing or matrixing would be inappropriate. Proposed change (if any):	Comment partially agreed - bracketing is covered under general considerations
271	17	Comment: maybe if a new technology is introduced into a standard process the validation could be required only for the new technology not the full product process at full scale. Proposed change: modify text to read "the introduction of a new technology … might result in the need for full-scale validation data of the new technology based on…"	Point noted: section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
273-278	9	Comment: Current text bullets read, • "Processes with critical steps such as lyophilisation, microencapsulation; • Processes where the physicochemical properties of the active substance or a key excipient (e.g., lubricant, coating agent) may give rise to processing or scale up difficulties, or stability problems during manufacture at larger scale for related products; • Any request for real time release testing;	Comment agreed – the documentation requirements in the guideline on real time release testing do not require validation data in the dossier. Section 6.2 states – the manufacturing process is, or will be, validated adequately (as evaluated on inspection). Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting

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		• Aseptic processing." We recommend deletion of line 277, "Any request for real time release testing;" from the above bulleted list. Real time release should not be considered as a "specialized or complex" process requiring process validation data be included in the initial dossier submission. In addition, if this recommendation remains in the guideline, it would create a strong disincentive for adoption of this new technology. Real time release can provide a higher assurance of product quality, relative to the more traditional end product testing regimes. Real time release testing is combining measurements and process controls and unlike the other 3 bullets which are manufacturing processes. Proposed change: The revised bullets would read, • "Processes with critical steps such as lyophilisation, microencapsulation; Processes where the physicochemical properties of the active substance or a key excipient (e.g., lubricant, coating agent) may give rise to processing or scale up	more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
274	17	Comment: it is not clear which physicochemical properties of the active substance or excipient should mean that a process is considered complex. (For example, it would be unusual in the extreme for a film coating agent to cause scale-up issues.) This guidance content appears to broaden the scope of presubmission full scale manufacture potentially significantly and without providing full clarity on what risks should be considered.	Comment not agreed – this is not a new requirement. Manufacturing processes can influence the stability of the drug product (e.g. APIs prone to oxidation).

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		Also it is unclear why stability is included here as stability is usually not linked to validation with registration stability for commercialisation being underwritten by the ICH program in the first instance. Proposed change: please reconsider this text and either clarify, refocus or omit this guidance text.	
277	17	Comment: it is not accepted that a process that uses an RTRT approach immediately is classified as a specialized process / complex product. There could be very similar processes that utilize RTRT that should not need this escalation of validation expectations.	Comment agreed – the documentation requirements in the guideline on real time release testing do not require validation data in the dossier. Section 6.2 states – the manufacturing process is, or will be, validated adequately (as evaluated on inspection)
277	19	Comment: Any request for real time release testing [resulting in a manufacturing process labeled as non-standard]. Labelling processes incorporating real-time release testing as "specialized or complex" and requiring commercial scale process validation for the initial dossier submission would create a strong disincentive for the adoption of RTRT. It is acknowledged in the scientific community as well as in the EMA guidance on RTRT that such approaches can provide for a higher assurance of product quality relative to traditional approaches that rely on end product testing. Creating more stringent requirements for enhanced approaches to assuring quality of pharmaceutical products is a direct contradiction to the goals of ICH Q8, Q9 and Q10 and will impede their adoption.	Comment agreed – the documentation requirements in the guideline on real time release testing do not require validation data in the dossier. Section 6.2 states – the manufacturing process is, or will be, validated adequately (as evaluated on inspection)

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		Proposed change (if any): Remove RTRT requests as a non-standard process.	
278	17	Comment: aseptic processing is listed as specialised process whereas it is more dependent on the experience of the manufacturer. Many processes are solutions and the process validation aspect is not so special. Proposed change: remove aseptic processing.	Point noted: section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
278-279	12	Comment: Align text with line 233-236. Proposed change (if any): Delete line 278 and change line 279 to: *"4. Non-standard methods of sterilisation and aseptic processing"*	Point noted: Section 8 has been amended to provide details of the information that a company could provide to justify that a process is standard for their manufacturing site putting more emphasis on the experience and GMP compliance of the manufacturing site rather than the type of process.
283	17	Proposed change: please add definitions for in-line, on-line and at-line (mentioned in line 84) and also off-line.	Comment agreed – see previous comments (line 45-46)
283	17	Proposed change: please add a definition for the term "enhanced approach" to align with the terminology used by ICH. This is understood to mean development via a Quality-by-Design model. Enhanced approach is mentioned in lines 45, 54, 74 and 81.	Comment agreed: a definition has been added
290-294	19	Comment: The definitions "Continued Process Verification" and "Continuous Process Verification" are very similar and thus confusing, even more so considering that "Continued Process Verification" is the name of Stage 3 to Process Validation	Partially agreed – terminology has been reviewed Continued process verification has been amended to on-going process verification. On-going process verification is now considered to

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		according to FDA. Proposed change (if any): Instead of using two definitions, use only one which would describe a unique harmonized approach instead of two potential parallel approaches.	fall under GMP and may be addressed in the update to Annex 15.
291	21	Proposed Changes: For the definition for 'Continued Process Verification', add the phrase 'through quality procedures and continuous improvement initiatives' to the end of the sentence.	Comment not agreed: not considered to be required.
307	17	Comment: the definition of High Impact Model is necessary but the definition provided may be sub-optimal as the phrase 'significant indicator of quality' may not differentiate models that are the sole indicators of quality from other models where a subsequent quality tests is conducted. Proposed change: revise the definition to read "A model can be considered high impact if prediction from the model is alone used to determine the quality of an attribute of the product."	Point noted: section has been removed, hence definition is not required.
318	18	Delete "and quality attributes" since by definition a specification includes the quality attributes (Q6A and Q6B).	Comment not agreed: definition has already been in use. Quality attributes can also address areas that are not covered by Q6A and Q6B.
319-331	17	Comment: If API were taken into scope, it would make sense to reference ICH Q11 here also. Proposed change: Add reference to ICH Q11.	Comment agreed: ICH Q11 has been included in the references.
319-331	17	Comment: Reference to Annex 15 is missing.	Comment agreed.

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		Proposed change: EUDRALEX Vol. 4 (EU-GMP), Annex 15	
332-363	13	Comment: this refers back to the outdated concept that three consecutive batches in specification demonstrate a validated process. We think that the concept of Continuous Process Verification needs greater emphasis, and therefore that some additional guidance is required at this point. Proposed change (if any): For all new processes, the application of continuous process verification should be used.	Comment not agreed – the traditional approach is still valid.
337-339	17	Comment: here it states the number of validation batches will usually be a minimum of 3 consecutive batches. In section 5.1, line 125 it states for other non-standard processes 1 or 2 production batches will suffice where these are supported by pilot scale batches. This should be stated in Annex 1. There is also no mention of standard methods of manufacture or conventional processes. If non-standard methods of manufacture can use 1-2 production scale batches, can it therefore be justified that standard (conventional) methods of manufacture may use less than 1-2 production scale batches where supported by pilot scale or other data? ICH principles provide opportunities to adopt more flexible approaches to achieving the point of commercialization. Alternative process verification approaches build upon process understanding and defined control strategy, utilizing data of late stage development/clinical batches, early	Point noted: Non-standard process are not relevant for annex 1 as the data will need to be provided in the dossier and annex 1 refers to the process validation scheme to be used where data are not provided in the dossier. Validation scheme should be performed on production scale batches.

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		commercial batches (as applicable). Current level of process understanding achieved by prior knowledge is considered and provides justification for an adjustment of the number of verification batches required. Proposed change: the text in lines 125-127 regarding other specialised non-standard processes requiring data on 1 or 2 production scale batches supported by pilot scale batches should be repeated / covered in Annex 1. In addition, guidance on standard processes requiring less than 3 production scale batches when supported by pilot scale batches should be given. There should be some emphasis on justifying the number of batches used.	
339	18	No information is given on criteria to determine the number of PV batches except it would "usually be a minimum of 3" batches. It is unclear whether a "default" of 3 is acceptable or whether further rationale is required. If statistical criteria are intended, it should so state.	Point noted: Data on a minimum of 3 should be provided. The actual number of validation batches to be manufactured is a GMP issue.
343-344	17	Comment: we recommend using the term critical process parameters. In addition, should CQAs be included? Proposed change: use ICH terminology for critical process parameters (CPP) and consider if CQAs should also be included.	Comment partially agreed – CQAs not required as it is the process that we are looking at.
345	17	Comment: it is unclear if a reference to the dossier can be made. Proposed change: Finished Product Specification (release) (References to the dossier)	Comment agreed – reference to the dossier is possible.

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345	8	Comment: It is unclear if a reference to the dossier can be made. Proposed change (if any): • Finished Product Specification (release) (References to the dossier);	Comment agreed – reference to the dossier is possible.
345	14	Comment: finished Product Specification to be included in the process validation scheme is unnecessary, since it is provided elsewhere in the dossier. Proposed change (if any): teference to the specification would suffice.	Comment agreed – reference to the dossier is possible.
360	17	Comment: this text suggests that "any changes" to manufacturing process in these cases requires prior approval. Assessors would not currently be notified of significant deviations in a process validation as this would be handled in the quality system / as an inspectional matter	Comment not agreed – any significant changes to the manufacturing process will need to be reported to the authorities. Deviations in the process validation would not need to be reported unless they trigger a change in the manufacturing process. The guideline reflects this.
360-361	8	Comment: it is no common understanding at present that major deviations are relevant before market submission. Proposed change (if any): Please clarify	Comment not understood.
361-363	20	Comment: the draft states "any changes proposed in the manufacturing process should receive prior regulatory approval by way of variation" however, specifying "prior" in this context may appear to be inconsistent with the Commission Regulation (EC) No 1234/2008 and supporting	Comment agreed: text has been amended to 'appropriate'.

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		guidelines regarding the process for handling minor variations identified as Type IA or Type IB. Proposed change (if any): consistent with lines 224-227 which specifically refers to the EC Guidance on Type I and Type II variations, we recommend revision to line 362 as follows, "any changes proposed in the manufacturing process should receive ~~prior~~ appropriate regulatory approval by way of the variation category."	
365-366	17	Comment: Additional monitoring should not be required where there is already continuous monitoring, as per the ICH definition. Proposed change: please remove this stated general need to conduct additional monitoring for the first commercial batches. Or provide additional clarification on what would be the expected if we are in a continuous verification mode	Comment agreed – this section has been reworded.
366	23	Comment: '*additional monitoring would be expected for the first commercial batches*' – suggest that instead, the level of monitoring implemented would reflect the level of knowledge; the level of monitoring would be reviewed periodically and adjusted if appropriate. Proposed change (if any):	Point noted: section has been revised so comment is no longer relevant.
369-372	17	Comment: **s**ince this section is titled "Continuous process verification", the term continuous processing could be confused for a shortened version of this term, as opposed to a continuous process where discreet batches may not exist.	Point noted: this section has been reworded.

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		Additionally, it is not clear what is meant by the phrase, ".. the stage where the commercial process is considered to be validated should be stated..". The term 'stage' could refer to a unit operation. Proposed change: it would be clearer to emphasize the nature of continuous processing in a separate section and to state that the expectation is to define at which point in time sufficient data has been collected to allow the process to be considered verified. In addition, should continuous processing get more of a mention all the way through this guide?	
369-372	8	Comment: this sentence is confusing. What is meant by "Continuous processing"? And who is allowed to call such a process validated, and when? How to submit this approach? Proposed change (if any): please rephrase and explain this sentence in more details to clarify it.	Point noted: this section has been reworded.
Sections 5.2, 5.3, 5.4	22	Comment: the guideline should help clearly advise when the transition from Continuous Process Verification (and/or) Hybrid Approach to Continued Process Verification should occur. Proposed change (if any):	Point noted: continued process verification is relevant in the commercial phase once continuous verification has been completed. Continued process verification has been amended to 'on-going process verification. On-going process verification is now considered to fall under GMP and may be addressed in the update to Annex 15.