14 July 2017
EMA/CHMP/QWP/104223/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft Guideline on manufacture of the finished dosage form'

(EMA/CHMP/QWP/245074)

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

Stakeholder no.	Name of organisation or individual
1	Association of the European Self-Medication Industry (AESGP)
2	Astra Zeneca
3	Bundesverband der Pharmazeutischen Industrie e.V (BPI), Germany
4	European Federation of Pharmaceutical Industries and Associations (EFPIA)
5	European Generic and Biosimilar Medicines Association (EGA)
6	Gilead Sciences International Ltd.
7	GSK
8	HERMES ARZNEIMITTEL GmbH
9	Mundipharma
10	Parenteral Drug Association (PDA)
11	PAREXEL International
12	SciencePharma (Poland)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We observe the tendency that more and more manufacturing information is requested in the regulatory application. As a consequence, many more variations have to be filed. The past guideline had a very pragmatic intent to limit variations; it stated "*it is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed description of the manufacturing process, apparatus and in-process controls should therefore be avoided.*" The same pragmatic intent should be carried to the current guideline. We believe this is also one of the main intents of ICH Q12 which is under development. The guideline should indicate which information is expected to be included in which section of module 3 i.e. which elements of the information are expected to be contained in 3.2.P.2 or sections of 3.2.P.3.	Comment noted. On the contrary to the observation stated in this comment, assessors throughout EU have observed a tendency for companies to provide less and less information in the manufacturing section to the point that there is little or nothing to assess. Therefore it is not the intention to go back to the statements of the previous guideline, as these statements have been misused in the past by some companies. The guideline focuses mainly on section 3.2.P.3.
2	The guideline seems to have quite a lot of extra detail over and above the previous guidance. Some is sensible and acceptable, however, the general concern from AZ is that for those 'standard' processes that are traditionally developed we avoid any new requirements to add additional burden to review and post approval action.	Comment noted. The aim is to ensure that important details, which can facilitate an appropriate assessment of the manufacture of the finished product, are included in the submission.
2	The additional requirements provided in the guidance around bulk packing and storage is already GMP requirements. Therefore AZ recommend that the EMA consider whether this is required in this guidance or there is a more general referral to GMP guidance so as not to add additional burden to review and post approval action.	Comment noted. For bulk product, the difference between GMP requirements and CTD Module 3 requirements has been carefully considered and amended where appropriate with GMP Inspector input. The basis for bulk product information comes from the current Q&A published on the EMA website.
3	The GMP systems are established and efficient in every single	Comment noted. The difference between GMP requirements

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	company since many years and inspected on a regular basis. There is neither plausible reason nor added value for a double control of the same information by GMP inspectors as well as by assessors during an application for marketing authorization and other regulatory procedures. Moreover, an inclusion of all information suggested in the draft into module 3 causes additional work and expenses for both authorities and manufacturers of the medicinal product without additional benefit. The draft will lead to a situation where even minor changes in the manufacturing process description (e.g. details of non-critical process description) or in the manufacturing environment will evoke the filing of variations with high amounts of paper-work and organisational constraints in the manufacturing processes. This is an additional challenge in the field of regulatory compliance and the opposite to the idea of “better regulation”. Especially for products that have been manufactured for many years there is no benefit to provide such detailed manufacturing process description that would have to be filed with each variation affecting the manufacturing process. Since the information required by this draft has already been documented and tracked in the framework of GMP before and GMP inspectors perform on-site assessments under real-life conditions a paper-based assessment by regulatory authorities based on module 3 or filing of variations is redundant. It will only lead to an increase of bureaucracy and will increase the manufacturing cost and the revenues of regulatory authorities – without any benefit for patients. **Comment and proposed change:** BPI strongly suggests not publishing this guideline.	and CTD Module 3 requirements has been carefully considered and any overlapping should only be minor. The guideline as proposed covers the basic information that should be provided in general to ensure an appropriate scientific assessment and should also be helpful to assessors as well to industry in preparing the dossier. It is not expected that this guideline will trigger higher numbers of variation since its basis should reflect current practice. The Suggestion not to publish the revised guideline is not accepted.
4	EFPIA welcomes the opportunity to provide comments on this updated guideline. EFPIA believes this guidance revision is important and the inclusion of	Comment noted.

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	some aspects of modern development and manufacturing expectations are welcomed. However, EFPIA has some concerns about the content and timing of the draft guideline. Detailed comments on specific sections are provided in this response, but the following general comments are considered significant and EFPIA requests their careful consideration by EMA.	
4	EFPIA questions whether the timing of the update to this guideline is ideal. This guideline considers elements such as the manufacturing process description and established conditions but is not clearly aligned to other related new guidance in draft such as the ICHQ12 guideline. EFPIA believes the agency should consider whether this guideline should be revised once other related guidance has been further developed. Guidance aligned with ICHQ12 concepts of established conditions on parameters included in the manufacturing process description and the associated change management expectations would be welcome.	Comment noted. The guideline has been revised in line with current information about ICH Q12 and it is not expected that the new paradigm described in ICH Q12 will be compromised by this guidance. The information provided is not in contradiction to ICH Q12 and it is not appropriate to delay one document in anticipation of completion of another.
4	The section describing the required level of detail for the manufacturing process description in P3.3 is considered very impactful, and EFPIA believes that this section requires further review. The text states that "*The same requirements apply to the level of detail in the manufacturing process description irrespective of the development approach*." EFPIA believes that this would not be an effective outcome of enhanced development where operating variability and criticality are known and understood, which should positively impact on post-approval change management. EFPIA encourages the agency to consider ensuring this section is aligned with considerations of established conditions currently under discussion within the ICHQ12 framework, where enhanced	Comment noted. The description of the manufacturing process should be provided in such manner that it can be followed and provide sufficient detail to allow evaluation by the assessor. All manufacturing steps should be included irrespective of whether these steps have been carefully scrutinised in development and found to be fully controlled. Please refer to the previous comment on ICH Q12 - see above.

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	development can lead to a differentiation in reporting categories. Overall, EFPIA believes that it is important that regulatory authorities globally are aligned on their expectations for P3.3, both in the number of parameters required and the change management expectations for this information. EFPIA also wishes the Agency to consider our position (ref 67.230) with respect to the Agency's draft Q&A EMA/689005/2017 on improving the understanding of manufacturing process descriptions.	It is understood that global alignment is welcome, however this is EU guidance and specific issues relating to the EU environment cannot be excluded.
4	The Annex example of a manufacturing process description is potentially unhelpful. For example, the Annex attempts to focus on differentiation between 'traditional' and (enhanced) QbD expectations but provides too simplistic a differentiation between the two parts of this spectrum. EFPIA believes that the term "QbD application" has a wide range of meanings since elements of QbD can be incorporated to different extents in different parts of the CTD. Additionally, we do not believe the content of the Annex provides appropriate guidance, even for the one dosage form type considered. The outcome from an enhanced approach to development can be different from product to product, and company to company, so it is not considered appropriate to suggest a single outcome. EFPIA highlights that the Annex example is not aligned with detail elsewhere within the guideline, nor with respect to the draft Q&A EMA/689005/2017. Overall, expectations for a traditional compared to a QbD application provided by the Annex are not clearly differentiated elsewhere in the text of the guideline We also note our earlier comments about the need for expectations for P3.3 to be aligned globally. EFPIA supports the EMA intent to link levels of understanding to	Comment noted. The annex has been revised in line with comments provided; however, it should be noted that it is difficult to provide examples which cover all situations and types of finished dosage forms but the general principles contained in the example should still apply.

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	differentiated expectations to process descriptions and their change management but requests that the Agency remove this Annex example from the updated guidance at this time. Future examples could be developed in collaboration with global regulatory authorities and industry, ideally within the framework of ICH.	
4	EFPIA further notes that the Annex example could be interpreted to imply that details of process development and risk assessment should be included within P3.3 and that such details should only be included in P2.	Comment noted. This is not the intention of the Annex and it has been revised as indicated above.
4	The introduction states that only product specific aspects of manufacture need to be described and included in the application and that *"general elements of Good Manufacturing Practice (GMP), (ref 3) should not be included".* In EFPIA's opinion, this position on GMP is not consistently applied in the draft guideline. EFPIA encourages the EMA to review the GMP elements in the guideline and consider which can be removed and provides specific comments to highlight GMP elements currently included. In addition, any potential contradiction of this guideline with existing EU GMP Guidelines should be carefully assessed and inconsistencies avoided.	Comment noted. The guideline text has been further revised to better cover mostly non-GMP aspects; however, in some instances, the provision of GMP elements is needed in the CTD module 3 to enable a better understanding of the company's position.
4	EFPIA supports that information about prolonged storage during manufacture be provided; however, EFPIA believes the section in the guideline on bulk storage needs further revision Whilst EFPIA acknowledges information is needed in the file by assessors to understand how risks from prolonged storage are discharged, such considerations are also part of GMP. Provision of data should be based on risk, and only applicable to	Comment noted. The section for prolonged storage has been further revised. It is agreed that the provision of data and justification should always be based on risk.

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	cases of prolonged storage which is not currently clear in the text as worded. Such data should scientifically justify the storage period, and not mandate information from 2 pilot scale batches as stated.	
4	In summary, EFPIA is concerned by several sections of this draft guideline, especially those closely linked to key elements of GMP, QBD, lifecycle management and ICH guidelines.	Comment noted. Concerns of stakeholder have been carefully considered during revision of the guideline.
5	No focus on GMP Should not lead to extra variations The EGA very much welcomes the new guideline on manufacture of the finished dosage form as it provides further clarification on the type and level of information that should be introduced in the CTD module 3 of the marketing authorisation application and appreciates the opportunity to comment on the draft guideline. The EGA would like to forward two general comments on the guideline. 1. The previous guideline stated that it is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed descriptions of the manufacturing process, apparatus and in-process controls should therefore be avoided. Although it is acknowledged that such statements may seem odd in guidelines and thus may be appropriate to be removed, the EGA is convinced that in order to create a fit for purpose regulatory system this principle should still be valid. The current draft is however not reflecting this principle and in some respects even the contrary. In line with guidelines that are currently been developed such as the ICH Q12 guideline, the EGA would like to highlight that focusing resources on high priority issues for patients is of key importance.	Comment noted. See above The avoidance of unnecessary variations is also an aim of t EMA; however; it is important that applicants do not misuse this statement in such a way that no or very limited basic structure of manufacture is provided in order not to be forced to submit variations at a future date. The aim of the revised guideline is to guide the applicants on the level of information needed to enable a thorough assessment. The guideline text has been further revised to better cover mostly non-GMP aspects; however, in some instances, the provision of GMP elements is needed in the CTD Module 3 to enable a better understanding of the company's position.

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	2. The EGA would like to note that although the guideline clearly states that only product specific aspects of manufacture need to be described and included in the MA-dossier, still several general elements of GMP are included throughout the guideline (e.g. line 87, .	
7	Update of this guidance to provide clarity on current expectations is appreciated.	Comment noted.
7	GSK fully supports the comments submitted by EFPIA on this draft guideline and appreciates the opportunity to provide further additional feedback for consideration by the Agency. We hope that our additional comments are helpful and provide further insight which may be of use to the Agency in finalising the guidance.	Comment noted.
7	The expectations for manufacturing processes for a traditional compared to enhanced development is welcomed. The differentiation exemplified in the Annex example between traditional and (enhanced) QbD applications is not clearly differentiated in the text of the guideline (e.g. sections 4.3 and 4.4). The principles exemplified in the Annex example should be clearly represented and aligned in the guidance text and the Annex example removed since an example is potentially misleading and too simplistic across the spectrum of traditional to enhanced development, for different or more complex dosage forms or for different company approaches.	Comment noted. To cover all the concerns raised, the text in the guideline and in the Annex has been further revised.
7	GSK supports development of separate guidance to detail the requirements for continuous manufacture outside the scope of this guideline update. GSK recommends this would be best developed as a new ICH Quality guideline.	Comment noted.
7	A number of sections within the guideline (e.g. batch size, batch definition, upper/lower limits on ingredient quantities) state	Comment noted.

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	"justification" required. Where appropriate, we recommend that the guideline states that the justification is expected in P.2. Pharmaceutical Development; this could be stated either in the introduction or where this is mentioned in the guideline for clarity.	
9	Mentioning other relevant guideline is very welcome. Issues of those guidelines should be stated verbally only if the cited guideline must be read differently in term of this guideline than stated in the cited guideline or if something needs to be highlighted especially for the manufacture of the finished dosage form.	Comment noted. The reference to other guidelines is an essential part of this document.
10	Throughout the guidance document reference is made to the "bulk product". It appears to be used differently in different sections. (See Line 223-225: any isolated material waiting forward processing and line 83: a drug product batch sub divided for final packaging.) In order to avoid any misunderstanding, definitions should be provided in the "Definitions" (see also comment to line 257).	Comment noted. The mention of "bulk product" has been revised throughout the guideline to address the concerns raised.
10	PDA recommends that the scope and wording of the guidance should be precise in order to avoid any misinterpretation. The wording as chosen in the draft ("chemical and herbal medicinal products") does not include all medicinal products that are regulated by Dir 2001/83/EC, (e.g. drug products containing semi-synthetic active substances). Also the conditional language "does not generally apply to radiopharmaceuticals; however the principles may be applied where relevant" can also lead to misunderstanding and confusion. PDA believes that having a clear scope for this guideline consistent with EU Directives is important for ease of use. See also specific comment to lines 49-56.	Comment noted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
29-30	10	Comment: Wording that requires clarification. Proposed change (if any): The note for guidance has been updated to reflect **the requirements as laid down in the current legislation (Directive 2001/83/EC, ref 1)** ~~changes~~ **and to follow** ~~to~~ the format and content of the Common Technical Document (CTD) Module 3 dossier.	Comment accepted. Text has been revised accordingly.
34&60	10	Comment: Clarify that reference is made to the marketing authorisation, not to the manufacturing authorisation. Proposed change (if any): However as stated in article 23 of Directive 2001/83/EC (ref 2) after a **marketing** authorisation has been issued …	Comment accepted. Text has been revised accordingly.
36-37	7	Comment: Guidance states that after approval, the authorisation holder should take account of scientific and technical progress to introduce changes. Expectations for updating parameters in an authorised traditional application to an enhanced (QbD) approach should be explicitly stated to ensure clarity. Given that the criticality of operational parameters may not be fully established for older products that were not developed using a modern (enhanced) pharmaceutical development approach, it would be burdensome to transition a traditional application to a QbD application. Proposed change (if any): The following statement is proposed for consideration:	Comment not accepted. The comment has been noted; however, the detailed information about consequences of using traditional or enhanced approach is not relevant for the Summary.

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		"When changes to an approved application are required, continuation with a traditional approach or updating the application to a QbD approach is at the applicant's discretion."	
38 - 47	3	1. Introduction: In the introduction it is explained that the guideline is intended to provide "*clarification on the type and level of information that should be included in the CTD module 3 of the MAA dossier with respect to the manufacturing process description.*" In 4. Manufacture it is stated that *"Only product specific aspects of manufacture need to be described and included in the MA-dossier; general elements of Good Manufacturing Practice (GMP) should not be included."* By reading the guideline it becomes obvious that many requirements on manufacture are not new but already covered by GMP requirements but so far have not been included in the CTD module 3 and thus in future fall under the variation system. According to the scope this guideline is also applicable for herbal medicinal products. Especially Traditional Herbal Medicinal Products are often in direct competition with food supplements and there are significant additional costs for manufacturers of registered products compared to the environment of food supplements that is less strictly controlled. This is also not in the sense of consumer safety. **Comment and proposed change:** BPI strongly suggests not publishing this guideline.	Comment not accepted. The sections highlighted in the comment do not support the proposal of not to publish the. The concerns regarding GMP vs. CTD Module 3 and manufacture of herbal products are noted; however they should not be addressed within the Introduction section of the guideline.
39-47	2	Comment: AZ recommend that a paragraph from the	Comment not accepted. The proposed text from the previous

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		previous guidance document ("Note for guidance on the manufacture of the finished dosage form, 1 April 1996") be included in section 1. **Proposed change:** AZ suggests retaining the following text ***"It is neither in the interests of the applicant or the authorities to have excessive detail in regulatory descriptions of processes as this would lead to large numbers of otherwise unnecessary post approval changes (variations). Very detailed descriptions of the manufacturing process, apparatus, and IPC should therefore be avoided."***	guideline is not appropriate for the revised guideline, the sufficient amount of detail has to be provided to reach conclusion during assessment and to appropriately describe a process. The word "excessive" in former guideline has led many companies to misinterpretation.
47	4	Comment: Proposed change (if any): Add specific reference to the guideline requirements for sterilisation processes.	Comment not accepted. The guideline on requirements for sterilisation processes is still under development. Hence, a reference could not be added.
48	4	There were no specifics called out for products such as pre filled syringes, autoinjectors. It is assumed that the expected information would be the same for these as is the sterile filing for vials and syringes…process description, validation, control strategy for device assembly. Could the guideline scope mention applicability to these. It should also be specified that the GL does not apply to vaccines.	Comment not accepted. The scope is considered sufficiently broadly described. The specific dosage forms will not be mentioned in the scope. Vaccines are considered as biological products and therefore the principles of this guideline are in general also applicable for them.
49-56	10	Comment: PDA recommends the following modification to the scope and wording in order to fully align with Dir 2001/83/EC and in order to avoid any misinterpretation. Proposed change (if any): "This guideline is applicable to	Comment not accepted. The proposal is noted; however, it is considered appropriate to mention specifically chemical, herbal, biological and radiopharmaceutical medicinal products, instead of making a reference to the Directive.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the manufacture of the finished dosage form of ~~chemical and herbal~~ medicinal products for human use **as are regulated by the provisions laid down in Directive 2001/83/EC apart from advanced therapy medicinal products (ATMPs)**. ~~The principles described are in general also applicable to biological medicinal products.~~ Due to the nature of ~~advanced therapy medicinal products (~~ATMPs~~)~~, the guideline is not applicable to these. ~~This guideline does generally not apply to radiopharmaceuticals; however, the principles of this guideline may be applied where relevant.~~	
50	4	Comment: It is stated that this guideline should also be applied to variations when changes to the manufacturing process are enacted. Pease clarify under which circumstances EMA will expect to receive the updated information to comply with this guideline	Comment noted. However, no action was taken as clarification on variations is not part of the text of this guideline.
53	4	Comment: Unlike the existing guideline, the scope of the updated guideline states that, "The principles in general are applicable" to biological medicinal products. However, the text reads as though the guidance has been written for small molecules so it is unclear how the guidance might be applied to biological medicinal products. Is it possible to clarify for biological product examples within the text.	Comment noted. However, the position of EMA is that the principles apply for biological products as well.
57-58	2	Comment: The sentence *"Application of this guideline to the manufacture of investigational medicinal products is*	Comment not accepted. The scope of guideline has been carefully worded not to add additional burden and it is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not intended, but the principles of this guideline may be applied." could be open to misinterpretation by Pharma and EMA, which could add unnecessary expectation/burden to clinical trials materials. **Proposed change:** AZ recommends removing this sentence. If the EMA still wish to include the sentence then AZ recommend the addition of the following wording ***"....for late stage registration studies."***	believed that principles of this guideline are acceptable for any manufacturing process. Information on manufacturing data required to support clinical trials is outlined the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.
63-65	4	Recommended change: "The requirements on the description of the manufacturing method in the CTD Module 3 of marketing authorisation dossier are described in Annex 1, Part 1 (section 3.2.2.3) to this Directive**,** and will be further elaborated in this guideline." Existing wording could be read to imply the elaboration provided by this guideline constitutes a requirement along with the Directive. Recommending changing the text to distinguish between the guideline and the directive. The requirements on the description of the manufacturing method in the CTD Module 3 of marketing authorisation dossier are described in Annex 1, Part 1 (section 3.2.2.3) to this Directive**. Guidance on what information could be included** is provided in this guideline."	Comment accepted. Text is revised.
70	1	Comment: For further clarification we recommend to replace line 70 with the following wording taken from QWP/486/95 - chapter 2, 7.4, 7.6.	Comment not accepted. GMP issues are not to be elaborated in this guideline.

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		Proposed change (if any): Non-product related elements of Good Manufacturing Practice (GMP) should not be included. Examples are qualification of key personals, cleaning procedures for the production equipment and areas, final packaging and labelling procedures, cleaning of primary packaging materials, details on production areas.	
71-77	4	It should be specified that stability testing sites, batch release sites, and storage facilities do not need to be listed. It is also assumed that site of batch release still remains in Module 1.2 versus Module 3.	Comment not accepted. QWP outcome: Information provided in the Module 1 should be in line with information in Module 3 in connection of manufacturing chain, therefore all relevant sites as listed in Module 1 should also be listed in Module 3. The text has been revised accordingly to provide additional clarity.
71-77	5	Comment: It is not appropriate to state all packaging, batch control and batch release sites as this will lead to various versions of module 2/3 in case of parallel submissions for different MAHs. This will increase work load for authorities and for applicant as different versions of module 3 have to be reviewed. It is sufficient to state packaging, batch control and batch release sites in the respective module 1 sections. Proposed change (if any): Section should be limited to bulk manufacturing sites.	Comment not accepted. QWP outcome: Information provided in the Module 1 should be in line with information in Module 3 in connection of manufacturing chain, therefore; all relevant sites as listed in Module 1 should also be listed in Module 3. The text has been revised accordingly to provide additional clarity.
72-77	2	Comment: There appears to be some repetition between the two paragraphs in the section (4.1. Manufacturers).	Comment not accepted. QWP outcome: Information provided in the Module 1 should be in line with information in Module 3 in connection of manufacturing chain; therefore, all

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		Proposed change: Suggest replacing the two paragraphs with ***"Only those sites that are involved in the manufacture and control of finished product until release need to be included. In addition, the company responsible for the final release of the product onto the market shall be specified."***	relevant sites as listed in Module 1 should also be listed in Module 3. The text has been revised accordingly to provide additional clarity.
73-74	1	Comment: The term "including contractors" should be eliminated. Management of contractors, especially those who are specialized on certain types of analytical tests, are covered by GMP with regard to the supervision of the reliability and qualification of contractors. Contractors that are included in the manufacturing license of a manufacturer should not be included in CTD Module 3. Otherwise it would be redundant and it would imply approval processes by the authorities which should be avoided. In addition, it should be clarified that (re-) packagers who only repack from one package size in another one or who exchange packaging components in the name and under direct supervision (agreement) of the MAH are not in the scope of this paragraph. Proposed change (if any): "The name, address and responsibility of each manufacturer should be provided."	Comment not accepted. QWP outcome: Information provided in the Module 1 should be in line with information in Module 3 in connection of manufacturing chain; therefore, all relevant sites as listed in Module 1 should also be listed in Module 3. The text has been revised accordingly to provide additional clarity.
74	3	**Comment and proposed change:** The use of external labs hast to be included in the section, but this requirement is covered by GMP	Comment not accepted. QWP outcome: Information provided in the Module 1 should be in line with information in Module 3 in connection of manufacturing chain, therefore; all relevant sites as listed in Module 1 should also be listed in

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		rules. BPI suggests to delete the wording " including contractors"	Module 3. The text has been revised accordingly to provide additional clarity.
75	5	Comment: This sentence is almost the exact same as in the old guideline, thus the terminology seems outdated. We propose to use terminology in line with draft Annex 16. Proposed change (if any): The ~~company~~ sites(s) responsible for batch certification of the finished product ~~the final release of the product onto the market~~ shall be specified.	Comment not accepted. The wording has been changed to "batch release" also in accordance with the terminology in Annex 16 of GMP.
79-80	4	Comment: In the case where a range of batch sizes is proposed, rather than including multiple batch formulae, it may be clearer to state the batch formula for an intended batch size along with the range batch sizes proposed. Proposed change (if any): The batch formula for the intended batch size should be stated. In case a range of batch sizes is proposed, the range should be stated, or the batch formula should be provided for at least the highest and lowest batch sizes.	Comment partially accepted. The wording has been revised as follows: "The batch formula for the intended batch size should be stated. In case a range of batch sizes is proposed, the range should be stated, and the batch formula should be provided for at least the highest and lowest batch sizes".
81 - 82	4	Comment: Lines 81-82 of draft guideline introduces potential for a range of batch sizes to be registered but references the Process Validation guideline for the justification required. Section 6 of PV guideline suggests that the range should be justified by confirming that the range of batch sizes does not impact the CQAs. This could be	Comment accepted. The text has been revised to be in accordance with the Guideline on process validation for finished products - information and data to be provided in regulatory submissions.

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		achieved through comparative batch data in the submission rather than provision of process validation data as may be implied by current wording. Proposed change (if any): Propose that this statement is clarified to 'An application for a range of batch sizes should be adequately justified as not adversely altering the CQAs of the drug product taking into account the guidance provided in as discussed in the guideline on process validation section 6 (ref 4).	
81	5	Comment: This section should be aligned with the PV Guidance Proposed change (if any): Ranges of batch sizes should be adequately justified taking into account if variations in batch size would not adversely alter the CQAs of the finished product.	Comment accepted. The text has been revised to be in accordance with the Guideline on process validation for finished products - information and data to be provided in regulatory submissions.
83-86	3	Comment and proposed change: If the bulk product is assembled into different presentations or packs, the production batch size should be defined by the original bulk before any division. When the length of the subsequent processes and assembly is considered critical (e.g. filling for aseptically manufactured products), the division pattern should be indicated. The division pattern should not be required to be indicated in general for processes considered critical. The validation protocols for all processes (including critical processes) are based on extensive risk evaluation covering the individual worst case scenarios	Comment not accepted. The information about division pattern is considered important to understand the manufacturing strategy. The text has been changed to better describe what information is needed.

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		of division pattern.	
84-86	1	Comment: division pattern is subject to GMP Proposed change (if any):	Comment not accepted. Basic information about division pattern is considered important to understand the manufacturing strategy.
84-86	2	Comment: Please confirm whether there is an expectation to include time limits for 'critical' processes. Proposed change: AZ considers time to be GMP relevant. Also, AZ recommends that the EMA considers adding additional clarification to help Pharma and EMA reviewers identify the critical stages associated with batch division.	Comment noted. The information is already considered sufficiently clear. Any time limits required in an application will be assessed on a case by case basis. The most obvious case where time limits are necessary to state and validate is for sterile products, especially aseptically manufactured products.
85-86	4	Can it be assumed this means time in solution (thaw to end of filling)? Please clarify the example.	Comment noted. The information is already considered sufficiently clear. Any time limits required in an application will be assessed on a case by case basis. The most obvious case where time limits are necessary to state and validate is for sterile products, especially aseptically manufactured products.
85 & 86	4	Comment: Further explanation could be given for expectations for indication of division patterns.	Comment not accepted. The information about division pattern is considered important to understand the manufacturing strategy. The text has been changed to better describe what information is needed.
87	5	Comment: The term "qualified industrial equipment" is not understood. Qualification is a GMP aspect, which is not in scope in this guideline. Probably full commercial scale equipment is meant, however, the current wording is	Comment partially accepted. The text has been revised: "The batch size for a product to be marketed should normally be compatible with production scale equipment. It should be sufficiently large to be representative of commercial manufacturing to enable demonstration of a state of control".

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		misleading and it is anyway difficult to provide a more specific definition on a general basis. Proposed change (if any): The batch size for a product to be marketed should normally be compatible with qualified industrial full commercial scale equipment. It should be sufficient to allow process capability to be established.	
87-90	12	Comment: It is fully agreed that batch sizes should normally be compatible with qualified industrial equipment. However it does not seem justified stating that “commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided”. There are many non-orphan medicinal products manufactured commercially at smaller scales. Proposed change: “The batch size for a product to be marketed should normally be compatible with qualified industrial equipment. It should be sufficient enough to allow process capability to be established. For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided (e.g. orphan drugs).”	Comment not accepted. Orphan medicinal products are already mentioned as a possible (but not exclusive) exception; with proper justification, other products might also be manufactured at a smaller scale.
88	4	Comment: The term ‘process capability’ has a number of meanings, many more complex (e.g. statistical process capability) than the presumed intent in this context. Recommend simplification of the text. Proposed change (if any): Suggest this text be altered to something simpler, such as “The batch size should be sufficient to represent and demonstrate robust	Comment accepted. Text has been revised: “The batch size for a product to be marketed should normally be compatible with production scale equipment and should be sufficiently large to be representative of commercial manufacturing to enable demonstration of a state of control”.

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		commercial manufacturing."	
88-90	2	Comment: The provision of a minimum batch size of 100 000 units is considered non representative for specialist therapies and niche products (e.g. Oncology). Proposed change: AZ recommends that the sentence "For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided (e.g. orphan drugs)" is deleted.	Comment not accepted. Orphan medicinal products are already mentioned as a possible (but not exclusive) exception; with proper justification, other products might also be manufactured at a smaller scale.
88 - 90	4	Comment: Limitation of commercial batch size to at least 100,000 units seems too restrictive. It should principally be allowed to make use of the full range of equipment capacity that may allow lower volumes than 100,000 units based on adequate process validation, if appropriately justified. Proposed change (if any): deletion of the sentence.	Comment not accepted. Orphan medicinal products are already mentioned as a possible (but not exclusive) exception; with proper justification, other products might also be manufactured at a smaller scale.
88-90	5	Comment: A commercial batch size for solid oral dosage forms could be less than 100.000 units also for non-orphan drugs, if justified. Proposed change (if any): For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification with risk assessment is provided (including critical points of the product, process and impact of the environment).	Comment not accepted. Orphan medicinal products are already mentioned as a possible (but not exclusive) exception; with proper justification, other products might also be manufactured at a smaller scale.
88-89	10	Comment: The link between sufficient batch size to demonstrate process capability and the stated 100,000 units in the example is unclear. Please consider	Comment not accepted. Orphan medicinal products are already mentioned as a possible (but not exclusive) exception; with proper justification, other products might

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		clarifying the process or consideration for determining process capability such as the use of statistical process capability indices.	also be manufactured at a smaller scale.
91-92	2	Comment: Please can the EMA confirm their interpretation of sub batch and also clarify why sub batch needs to be stated. AZ have a concern that if a manufacturing site has 2+ manufacturing lines for a specific product, which involve differing scales of equipment with 'compatible and qualified industrial equipment' and the new product has registered scale ranges, to provide flexibility to meet changes to market demand (e.g. assets provided by a multi-product facility), this may result in reduced manufacturing flexibility and increased regulatory burden. Proposed change: If it is the EMAs expectation to require disclosure of all sub batch combinations for drug product, please consider providing an illustrated example or wording to clarify what instances sub batching needs to be described.	The comment has been partly accepted. However, it is important that information on the batches used in the dossier is retained.
91-94	1	Comment: Number and size of sub-batches should be variable analogous to batch size range, they are sufficiently controlled by GMP Proposed change (if any): Sub-batches may be prepared and combined for subsequent processing or a batch may be sub-divided towards the end of the process to reflect equipment processing capability, this should be clearly indicated.	See above

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91-94	3	Comment and proposed change: We suggest to delete “If sub-batches are prepared and combined for subsequent processing, their formulae and the number of sub-batches per intended batch size should be stated. In addition, if a batch is sub-divided towards the end of the process to reflect equipment processing capability, this should be clearly indicated. The number of sub-batches per intended batch size should be justified.” BPI suggests deleting this sentence as it reflects a matter of GMP. Furthermore, for medicinal products that have a variable range in batch size the division pattern for the different pack sizes (e.g. 6 ml to 10l) is not predictable. Fixing the division pattern would raise the logistic effort in production planning and it will impossible to react on the market requirements adequately. As a result, companies would produce pack sizes that cannot be sold. It has even a regulatory impact, if Agencies require variations for adequate batch sizes or pack sizes. This will enhance bureaucracy to react flexible on the market. But the manufacturing process itself is validated and controlled and documented by GMP requirements and inspected by local authorities. There is no need for further regulation in this guideline. Comment and proposed change: Throughout the guideline: We suggest to delete that type and capacity of equipment should be stated. Description of only general	See above

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		principles of type of equipment is appropriate here – to reduce the need of additional work /variations in future.	
91 - 94	4	Within the scope of manufacturing and the use of sub-batches it should be sufficient to provide the maximum number of sub-batches instead of providing a formula of those sub-batches. Depending on e.g. capacity reasons the batch formula shouldn't alter and is controlled via GMP. If there is a range of sub batches the minimum and maximum number to be used during routine manufacturing could be mentioned. Proposed change: If sub-batches are prepared and combined for subsequent processing, the minimum and maximum number of sub-batches per intended batch size should be stated. In addition, if a batch is sub-divided towards the end of the process to reflect equipment processing capability, this should be clearly indicated.	See above
91-94	5	Comment: The same term 'intended batch size' is used for both a 'super batch' from combined sub-batches as well as for the batch that will be divided into 'mini-batches'. We would welcome guidance on acceptance criteria as well as guidance in the GMP guidelines (e.g. in the GMP Q&A section) on the batch numbering. The EGA would also like to address that if a product is initially granulated or coated in a number of sections and is subsequently transferred to a larger equipment	See above

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		and granulated or coated in one section, the process is re-validated, but should this also be considered as a regulatory change if the batch size remains unchanged or is within the approved range? And if a common granule / blend is produced and sub-divided to produce batches of different strengths and eventually a separate granule / blend is produced for each strength, the process is re-validated, but should this also be considered as a regulatory change if the batch size remains unchanged or is within the approved range? The EGA would also like to highlight that a range of numbers of sub-batches should be allowed. Proposed change (if any): The EGA would like to propose to change this section so as to allow changes in the number of sub-lots within manufacture, as long as any changes are assessed through a formal risk assessment and if necessary, process re-qualification. If sub-batches are prepared and combined for subsequent processing, their formulae and the range of number of sub-batches per intended batch size should be stated.	
95	4	The request for “expected period of time for a campaign” is potentially not the most scientifically relevant variable. Consider removing this requirement, and provide separate guidance for continuous	Comment noted. Text has been revised.

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		manufacturing which considers other significant factors.	
95-97	1	Comment: In case of continuous manufacture the expected batch size of one campaign may vary, definition in CTD Module 3 may lead to unnecessary variations. Proposed change (if any): In case of continuous manufacture, the information about batch size in traditional terms might not be relevant; however information how a batch is defined should be provided. The expected size of one campaign (e.g. period of time) should be stated, indicating it as a range is acceptable.	Proposal accepted. The text has been revised as proposed.
96-97	5	Comment: The EGA proposes to include the quantity of product as an example of the size of one campaign (line 97). Proposed change (if any): The expected size of one campaign (e.g. period of time, quantity of product) should be stated.	Proposal accepted. The text has been revised as proposed.
98	1	Comment: For granulation liquids, solvents, gases and coating suspensions the amounts used during manufacture are variable, therefore stating the amounts may lead to unnecessary variations Proposed change (if any): The names, quantities and reference to the quality standards of all ingredients used in the course of the	Comment accepted. The text has been revised as proposed.

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		manufacture should be stated. This includes ingredients which are removed from the product during the production process, such as granulation liquids, solvents and gases. For the latter ingredients, expressing the quantity as a range may be acceptable.	
98	4	Comment: The reference to the quality standards of drug substance and excipients is already included in P.1 and P.4 sections of the submission. This should not be part of the P.3.2 section as well, as it seems redundant to add the same information at multiple locations in the dossier and complicates post approval change management. Proposed change (if any): delete "reference to the quality standards of all ingredients"	Comment not accepted. It is considered adequate to include reference to quality standards both in 3.2.P.3.2 and in 3.2.P.1.
100	4	Comment: Clarification is sought on whether this provision includes gases that are used for safety reasons only (e.g. nitrogen for explosion prevention)? Proposed change (if any): Add list of exceptions to current wording, e.g. "[…] such as granulation liquids, solvents and gases, excluding materials used for safety purpose only (e.g. nitrogen for inertion)."	Comment not accepted. E.g. nitrogen for explosion prevention is a very rare case and need not be mentioned in the guideline.
101	4	Comment: Please improve understanding by avoiding a confusing "may not always" phrasing Proposed change (if any): Ingredients that "can optimally" be used	Comment accepted. The text has been revised.
Lines 102-103	4	Recommended change: "Formula overages must be clearly indicated in quantitative terms and justified in the pharmaceutical development section of the dossier." Recommended clarifying that this is referring to formula overage.	Comment accepted. The text has been revised as proposed.

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104	4	Comment: As written, this section contrasts the previous version of this Guideline, where definition of ranges of ingredient quantities is need not always be justified. Proposed change (if any): Reword to reflect the existing guideline: “In justified cases, upper and lower acceptance limits for the actual quantities of each ingredient wider than typically considered acceptable (95-105% of nominal for active ingredients and 90-110% of nominal quantity for excipients) could be stated.”	Comment noted. The sentence has been reworded for clarity.
104-105	1	Comment: Acceptance limits of 95% to 105% for active ingredients and 90% to 110% for excipients are acknowledged for a long time. This should be mentioned explicitly according to the previous version of the guideline. Please add the following sentence taken from QWP/486/95 – chapter 3. Proposed change (if any): For active ingredients these acceptance limits should be within 95% to 105% of the nominal quantity. For excipients, acceptance limits of 90% to 110% of the nominal quantity are accepted without further justification.	Comment noted. The sentence has been reworded for clarity.
104-105	2	Comment: AZ recommend that wording from the previous guidance (“Note for guidance on the manufacture of the finished dosage form, 1 April 1996”) is used in place of “In justified cases, upper and lower acceptance limits for the actual quantity of each	Comment noted. The sentence has been reworded for clarity.

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		ingredient could be stated." Proposed change: AZ suggests retaining the following text "For APIs and excipients, contents of 95%-105% or 90%-110%, respectively are acceptable limits without further justification. Wider ranges can be accepted with justifications."	
104-105	8	Comment: Lines 104-105 should include the sentence of the former guideline QWP/486/95 on the acceptable ranges of active ingredients and excipients. Proposed change: "For active ingredients these acceptance limits should be within 95% to 105% of the nominal quantity. For excipients, acceptance limits of 90% to 110% of the nominal quantity are accepted without further justification."	Comment noted. The sentence has been reworded for clarity.
106	4	The justification for the Assay calculation should belong in the process description, not necessarily in the batch formula.	Comment not accepted. It is considered suitable to include the assay calculation in the batch formula.
114-5	4	Comment: "In case a design space is proposed, this should be presented in a transparent manner." It is not clear exactly what is meant by this sentence, so suggest sentence is reworded. Proposed change (if any): If a design space is proposed, then this should be clearly described.	Comment accepted. Text changed accordingly.
114	5	Comment:	Comment partially accepted. See accepted previous

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		The guideline should be consistent with ICH Q8 Proposed change (if any): **Reworded:** In case a design Space is proposed, this should be presented as per ICH Q8 Guidance.	comment.
116-117	1	Comment: Batch sizes are already mentioned in batch formula, and equipment sizes may vary depending on batch size, any change would provoke an unnecessary variation. Proposed change (if any): It is important that the process descriptions are comprehensive, suitably detailed and describe process steps in a sequential manner including equipment type(s) where appropriate.	Comment noted. The text has been revised to include “working capacity” instead of “size(s)”.
116-120	1	Comment: To avoid misunderstandings it should be clarified, that a comprehensive process description is only requested for product specific parameters (see line 69 of the present guideline). Proposed change (if any): For product specific aspects the process descriptions should be comprehensive, suitably detailed and describe process steps in a sequential manner including batch size(s) and equipment type(s) and size(s) where appropriate.	Comment not accepted. It is implicit that the description of manufacturing process is product specific.
116-117	5	Comment:	Comment noted: Sentence has been changed. The focus has

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		Equipment types may be specified e.g. high shear mixer but why should equipment size/s? Stating the size of the equipment during the development phase is not acceptable, implying too many rigidities and limitations for future manufacturing. The type of equipment and in process parameters already sufficiently describe the manufacturing process. Details can be provided during process validation prior to product launch. Proposed change (if any): Please remove reference to the equipment size, The section could focus more on the need of a suitable risk assessment to justify any changes in equipment size.	changed from size of the equipment to capacity
116-118 157-158	11	Comment: With regard to the description of the equipment, applicants can provide the level of detail including equipment model and number. In these cases, when the equipment is replaced with another model, applicants have to file variations to reflect this change in the dossier. From both a time and cost effective purpose, the filing of this minor variation can be avoided if a clause is include in the guideline; refer to proposed change below. Proposed change (if any): Description of equipment model and serial number is not required/necessary.	Comment accepted.
117, 305 and 362	4	Comment: The apparent requirement for equipment size/capacity, in addition to the registered batch size, does not seem to augment regulatory oversight and scientific	Comment noted. “Size” deleted and “working capacity” added in accordance with M4Q (R1) page 13.

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		understanding and, contrary to what is stated in line 33, does introduce a new requirement. A routine requirement to register equipment capacity could trigger a significant increase in the number of post-approval variations to register the installation of new equipment and could serve to deter manufacturers from installing more modern equipment. Proposed change (if any): The level of detail should be commensurate to the criticality of the equipment and the unit operation.	
119	1	Comment: Frequency of in-process controls for campaign production depends on batch size, any change would provoke an unnecessary variation. Proposed change (if any): For continuous manufacturing emphasis should be given on frequency of in-process controls and it should be clearly stated when the release testing is performed.	Comment noted. Text has been revised.
119-120	2	Comment: The EMA state *"emphasis should be given to frequency of in-process control"*, AZ believe this counters the principals of continuous process verification where in-process monitoring plans could be adjusted based on increased product understanding. In a sense this could also reduce manufacturing flexibility if the same in-process control frequency is expected across accepted and or registered manufacturing scale ranges. **Proposed change:** Please clarify whether a quantified in-process sampling frequency is required for both conventional batch and continuous manufacture.	Comment noted. See above

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120	4	Comment: The text states “it should be clearly stated WHEN the release testing is performed.” It is unclear what is expected here. Recommend text is clarified. Additionally, information on the frequency of in-process controls is a new requirement. Proposed change (if any): “Emphasis should be given on frequency of critical in-process controls and it should be clearly stated how release testing is performed / how product release decisions are made.”	Comment noted. Text revised partly according to the comment.
121-122	4	The text states: “The manufacturing process description should be adequately justified in particular **any** process operating conditions. Reword to: Process operating conditions or parameter ranges in the manufacturing process description should be adequately justified.	Comment partly accepted. The sentence has been reworded.
121-122	8	Comment: The wording with respect to numerical values for process operating conditions (target values and ranges) may cause authorities to request a level of details that would lead to avoidable variation applications while not adding safety to the pharmaceutical product. Due to common technical limitations of industrial manufacturing processes and measuring systems, parameters like temperatures, volumes, weights, reaction times, flow rates etc. will *always vary* to a certain degree during actual production. Setting explicitly single “target values” instead of ranges would in numerous cases not be reasonable neither from	Comment noted. Text and Annex have been revised to take this issue into account.

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		technical point of view nor from common scientific and process understanding. Additionally, the guideline text does not clarify to which extent one may deviate from a target value without facing regulatory non-compliance issues and creating the need for a variation request. Proposed change: It should be made clear that for reasons of common production practice, technical limitations and scientific process understanding, it is reasonable to indicate ranges or upper/lower limits for certain process parameters. It should be explicitly mentioned that this does not only apply for QbD applications. Lines 121-122 should read “The manufacturing process description should be adequately justified by development, in particular any process operating conditions or exceptionally wide ranges.” “Exceptionally wide range” should be exemplified.	
122	4	Comment: Not clear what ‘process operating conditions or *ranges’* mean? Terms used are not consistent with Annex where target value or ranges are described and not aligned to ICH terms to describe parameters (PAR etc). Also inconsistent with terminology used elsewhere in guideline (e.g. lines 129 and 161 (target values or ranges), lines 213 and 130 (range), line 138 (process parameters settings) etc). Please review for consistency. Also see our position with respect to the Agency’s draft Q&A EMA/689005/2017 on	Comment noted. Consistency of terms throughout guideline and Annex has been checked.

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		manufacturing process descriptions.	
122-124	1	Comment: This is subject to GMP Proposed change (if any): Please remove.	Comment noted. See revisions below.
122-123	3	**Comment and proposed change:** We suggest to change the wording as follows: "~~In addition, and~~ Only where relevant, any required environmental conditions during manufacture should be stated e.g. low humidity for an effervescent tablet." **Rationale:** Everything else is a matter of GMP	Comment partly accepted. The text has been revised as follows: "Accepted text: Where specifically relevant for the product, any required environmental conditions during manufacture should be stated e.g. low humidity for an effervescent tablet."
122	7	Comment: Not clear what 'process operating conditions or ranges' mean and terms are not consistent with Annex where target value or ranges are described, differentiated for traditional compared to QbD applications, and not aligned to ICH terms of PARs, design space, etc. Also inconsistent with terminology used elsewhere in guideline (e.g. lines 129 and 161 (target values or ranges), lines 213 and 130 (range), line 138 (process parameters settings) etc). For traditional authorised applications our assumption is that parameter values remain as justified and approved originally. For changes and new applications we would expect these to be adequately justified.	Comment noted. The terminology has been revised to be comparable throughout guideline.
123	4	Proposed change: change 'effervescent tablet' to	Comment not accepted. The "effervescent tablet" is

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		'humidity-sensitive product'	considered to serve as a suitable example.
126-129	1	Comment: The word "critical" sets focus on those process parameters and target values or ranges which have an impact on Critical Quality Attributes (CQAs). This is in line with the example in the Annex of the guideline where it is stated that not all process parameters need to be described, e.g. based on the nature of the drug substance, the complexity of the dosage form and the complexity of the process. Proposed change (if any): To make the process fully understandable and to allow assessment of the validity of the process validation studies/ validation protocol to support the claimed manufacturing process, all critical steps in the process should have the necessary detail in terms of appropriate process parameters along with their target values or ranges.	Comment not accepted. Limitation to critical parameters is not accepted. Lines are partly revised according to comments below.
126-127	10	Comment: A validation protocol is generally not submitted as part of a dossier and should therefore be deleted in the sentence below. Proposed change (if any): To make the process fully understandable and to allow assessment of the validity of the process validation studies~~/ validation protocol~~ to	Comment is not accepted. However, text has been revised for clarity.

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		support the claimed manufacturing process, (…).	
128	5	Comment: Please clarify all possible parameter value types Proposed change (if any): **Reworded:** .., all steps in the process should have pre-defined parameters with values being fixed or a range or a limit.	Comment noted. The text has been partly revised.
130-132--> 133-134	4	Comment: Some additional guidance on level of information/rationale required for biological medicinal products will be useful. Could some specific text be provided?	Comment partly accepted. Proposal is to delete: (e.g. biotech products…), therefore no additional guidance needed.
130-132	8	Comment: The wording with respect to numerical values for process operating conditions (target values and ranges) may cause authorities to request a level of details that would lead to avoidable variation applications while not adding safety to the pharmaceutical product. Due to common technical limitations of industrial manufacturing processes and measuring systems, parameters like temperatures, volumes, weights, reaction times, flow rates etc. will *always vary* to a certain degree during actual production. Setting explicitly single “target values” instead of ranges would in numerous cases not be reasonable neither from technical point of view nor from common scientific and process understanding. Additionally, the guideline text does not clarify to which extent one may deviate from a target value without facing regulatory non-compliance	Comment acknowledged. Text has been amended to reflect the current thinking.

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		issues and creating the need for a variation request. It is not clear what is meant with the statement that "wide acceptance ranges" "generally" require a more thorough discussion (lines 130-132). It should be exemplified what ranges would be understood as being "wide", and when a more thorough discussion would be needed. Proposed change: It should be made clear that for reasons of common production practice, technical limitations and scientific process understanding, it is reasonable to indicate ranges or upper/lower limits for certain process parameters. It should be explicitly mentioned that this does not only apply for QbD applications. Lines 130-132 should read "The description of a manufacturing process with exceptionally wide ranges (or described only by an upper or lower limit), may require a more thorough discussion and/or scientific rationale in the manufacturing process development section." "Exceptionally wide range" should be exemplified. "May" instead of "generally" enables an assessor to judge case-by-case before the background of the specific process and with respect to a certain parameter whether a detailed discussion to support a reasonable range would be required or not.	
130	7	Comment: The extent of scientific rationale required to justify wider acceptance ranges should also be linked to the criticality	Comment acknowledged, however the proposed change is not endorsed. The focus should not be on CPP and critical steps only.

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		of the parameter and/or operation and this should be added to line 130. Proposed change (if any): “The description .... with wide acceptance ranges ..... for critical process parameters (CPP) and/or critical steps generally requires more thorough justification.....”	
133	1	Comment: For standard processes this should be explicitly not required, since any deviations are covered by deviation and OOS management. Proposed change (if any):	Comment noted; it is considered clear that this is not an issue for standard processes.
133-135	1	Comment: This topic (deviations from approved manufacturing processes) is subject to a corresponding standard operating procedure (SOP). SOPs are not part of the dossier. Proposed change (if any): Please specify that in these more complex cases SOPs do not have to be provided however.	Comment noted; SOPs are not expected to be provided in the dossier.
133-135	2	Comment: AZ understands that handling of “accidental” deviations is covered by GMP (EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines). A request to provide “accidental deviations” could be impractical if the EMA is suggesting Pharma provides all foreseeable examples.	Comment noted but not accepted. It is acknowledged that accidental deviations are handled within GMP; however; for more complex cases, additional information needs to be provided in the CTD Module 3 to enable the understanding of how deviation(s) will be investigated and addressed.

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		Proposed change: AZ recommends that this text is removed.	
133-135	4	"In some more complex cases (e.g. biotech products, use of models for process control, continuous manufacturing processes), information of how accidental deviations from the approved manufacturing process will be managed can be helpful to assure that the intended quality of the product is retained." Recommend deleting this paragraph as it contradicts information on lines 69-70 that GMP aspects should not be included. Also, given that many biotech products are solution products, we do not consider such biotech products to be complex. Proposed change (if any): Please remove biotech products as an example of 'more complex' products.	Comment accepted. The biotechnological products have been removed from the example.
137-141	1	Comment: Only critical process parameters should be included in the CTD Module 3, any amendments regarding uncritical process parameters may lead to unnecessary variations Proposed change (if any): If the result of such full scale study is not available at the time of submission, it is expected that critical process parameters' settings identified during manufacturing process development are laid down in the process description. In the event that any changes are required to the registered critical process parameters as a result of full scale process validation studies, then these changes should be sought post	Comment noted; however, the proposal is not accepted. In line with the current definition of process validation (see definition below), the focus should not exclusively be on critical steps. "Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."

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		approval by way of variation, in accordance with the variation Regulation (ref 5, 6).	
137-139	5	Comment: The previous guideline has stated the following: “It is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed descriptions of the manufacturing process, apparatus and in-process controls should therefore be avoided.” While it is acknowledged that such statements may seem odd in guidelines and thus may be appropriate to be removed, however, knowing the backlogs in processing variations it is believed that this principle is still valid. The current draft is quite the contrary in this respect, and even if parameters on full production scale is not known, it expects that “process parameters' settings identified during manufacturing process development are laid down in the process description”. In addition to more details required, the current wording excludes making use of e.g. past experience on scaling up from pilot to commercial scale. Process parameters laid down pre-submission prior to any scale-up activities may require fine-tuning on scale-up. The requirement to submit variations, possibly supported by stability data, may result in sites accepting a sub-optimal process to avoid the need to submit variations and await approval which apart from being costly and time-consuming, could result in a delay in	Comment not accepted. Although the concern of submitting unnecessary variation is understood, it should be noted that the process description at time of submission should include all relevant data, including setting of process parameters. Prior knowledge of standard process can help to set the process parameters in sufficient way without the need of further changes. A type IA notification would in most cases be sufficient for such changes.

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		launch / first market supply. Proposed change (if any): Instead of requiring “provisional” parameters, a more flexible approach should be acceptable, especially in case of well-established, standard manufacturing processes.	
139	5	Comment: This part of the guideline should be in line with the EMA PV guideline: Proposed change (if any): **Reworded:** In the event that any changes are required to the registered critical process parameters, then these changes should be sought post approval by way of variation, in accordance with the variation regulation (ref 5,6). If the critical process parameters investigated during development of design space have not been shown to be scale independent and the process has been validated using traditional process validation, design space verification would be required.	Comment not accepted. The word “critical” is not stated in the extract from the process validation guideline.
142-143	2	Comment: AZ understand that the EMA is requesting the provision of more information about manufacturing duration, intermediate hold times and transportation conditions. AZ suggests the EMA clarify what instances or examples of ‘manufacturing durations, hold times and conditions during transport’ need be provided. It would also be useful to understand EMA expectations on the content of the filing regarding durations versus expectations placed by GMP (EudraLex - Volume 4 Good	Comment noted, the proposal to delete the information in brackets has been accepted; however; it is referenced in the guideline.

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		manufacturing practice (GMP) Guidelines). **Proposed change:** AZ recommends the removal of the text in brackets.	
142-144	3	**Comment and proposed change:** BPI suggests deleting "Every drug product manufacturing process (including manufacturing durations, hold times and conditions during transport) has an associated control strategy. The control strategy should be outlined based on development studies." **Rationale:** This proposed requirement is redundant since it is matter of GMP and an appropriate control strategy is confirmed by GMP process validation and by compliance with the product specification finally to be confirmed for each production scale batch.	Comment not accepted. Control strategy is not only a GMP matter and should be part of the CTD Module 3. It is not stated explicitly that this information must be part of description of manufacturing process: it is stated the connection should be acknowledged.
142-143	5	Comment: Please clarify what is meant by manufacturing durations? Is this the duration of the process from dispensing to packaging? Proposed change (if any):	Comment noted. This issue has been further discussed in other chapters.
142-149	5	Comment: The principles and requirements of ICHQ8 provides details on the data expected within the regulatory submissions and the draft guideline should adhere to the requirements of ICH and not require data excessive of what has been established in ICHQ8	Comment not accepted. It is not agreed that ICH Q8 provides details on the data expected, it rather provides general information. The information requested in this guideline does not contradict ICH Q8.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
143-144	4	"The control strategy should be outlined based on development studies." Is this statement on control strategy located in the correct section? Please review this paragraph to ensure it is clear. Move paragraph may be better included in another section/subsection For example, the control strategy could be included in other sections such as P2, or P3.4.	Comment noted. It is not stated in the revised guideline that control strategy must be part of the description of manufacturing process, but it should be clear from description that the control strategy, outlined in the development section, is followed in manufacture.
143-145	6	Comment: The control strategy should be based on GMP expectations and not necessarily contained in the filings.	Comment not accepted. Control strategy is part of development and manufacture of finished product and therefore should be mentioned in the dossier.
150	1	It should be clarified that non-product related elements of GMP need not to be included. The following wording is taken from the previous guideline QWP/486/95 – chapter 4. Proposed change (if any): If the consistent quality can be fully safeguarded by the implicit production under GMP production and testing of the finished product at release, description of manufacturing process need not to be comprehensive, and apparatus and in process-controls need not to be described.	Comment not accepted. The statement in the previous guideline has been misinterpreted; therefore, the wording has been modified. It is however clear that non-product related elements of GMP need not to be included.
151-153	5	Comment: Consistent quality of a product can be safeguarded by validating manufacturing processes and describing the manufacturing process in detail in the batch manufacturing instructions without the need to include	Comment not accepted. The information about manufacturing process has to be submitted in sufficient detail to be assessed and understood. The level of detail as given in the master batch record is not expected to be provided in the CTD Module 3.

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		the same level of detail in registration dossiers. Proposed change (if any):	
154-156	3	**Comment and proposed change:** *…irrespective of the development approach, i.e. if the product has been developed by the traditional or enhanced approach*. BPI companies raise the concern that the requirements of very detailed information regarding the description of the manufacturing process (traditional versus enhanced approach) will be in contradiction to the concept of quality by design. BPI companies raise additional questions that should be clarified in the context of this guideline: Will the method of parametric release / real-time release be regulated by this guideline explicitly or by Annex 17 of GMP-Guidance? Will it be possible to make use of both methods (traditional release and parametric release) in parallel, so it can be decided batch by batch which method shall be used?	Comment noted. The information about manufacturing process has to be submitted in sufficient detail to be assessed and understood whatever the approach taken for the pharmaceutical development; this is not in contradiction to the concept of QbD. Depending on the level of process understanding gained during development and also on the control strategy, the way the information is presented may be slightly different and the manufacturing process will reflect any justified and supported flexibilities when an enhanced development approach has been followed e.g. wide ranges established on a multivariate basis. The method of parametric release / real-time release is not regulated by this guideline explicitly. The use of traditional release and parametric release in parallel, as described in the comment, is not endorsed by this guideline.
154-156	10	Comment : This text in line 154-156 "*The same requirements apply to the level of detail in the manufacturing process description irrespective of the development approach, i.e. if the product has been developed by the traditional or enhanced approach"* seems to contradict the examples given at lines 351 and 355. Please consider a single example at line 351 that	Comment noted; however, no contradiction is foreseen. A comment has been added in the examples (Annex) to clarify the point.

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		accounts for criticality. Proposed Change: PDA suggests that no distinction between QbD and non-QbD should be made as is stated in line 154.	
155	5	Comment: This part of the guideline should be in line with with ICH Q8 Proposed change (if any): **Reworded:** .., i.e., if the product has been developed by the minimal approach or enhanced, Quality by Design approach	Comment accepted. Wording has been changed accordingly.
157	1	Comment: Operation principle should only be included in CTD Module 3 for critical unit operations; otherwise unnecessary variations will be required. Proposed change (if any): The operating principle for the equipment used should be described for each critical unit operation.	Comment not accepted. The operating principle for simple and non-critical steps is also important in the description of manufacturing process. See also answer below.
157-158	3	**Comment and proposed change** The operating principle for the equipment used should be described for each unit operation. The type of equipment should generally be stated (generally reference to “Suitable equipment” is not acceptable). BPI is of the opinion that a more general description of the equipment should be possible by	Comment noted. Text should remain as it is. General information for simple devices in a way “stainless steel vessel” would be accepted and is not in contradiction of the guideline text.

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		using the trailer “or equivalent” or filing the particular equipment as an example (“e.g.”). Especially for “unit operation” and “type of equipment” the filing in the dossier should be in this way that there still is a possibility to use alternative, equivalent and qualified equipment. A more general description like “stainless steel drum/ vessel” (without filing more specifics) should be sufficient.	
157- 159	4	Comment: CPMP/QP/486/95 previously stated ‘..*Very detailed descriptions of the ..... apparatus.....should not therefore be included*.’ This wording should be added to the updated guideline. Also, the level of detail provided should be commensurate to the criticality of the equipment and the unit Proposed change (if any): *Very detailed descriptions of the apparatus should not be included*.’ but the operating principle for the equipment used should be described for each unit operation.	Comment noted. See answer just above.
159	4	The extent of information required around the “type of equipment” is not clear. Different parts of the guideline provide different levels of detail. What is intended by ‘type’ in addition to ‘operating principle’? In some instances these terms appear used interchangeably whilst Annex example gives both but type is aligned with capacity. Additional clarification would be welcome. operation.	Comment noted. The text has been amended for better clarity. In the Annex, the terminology retained is “type of equipment”, and has been amended to delete the idea of capacity. The operating principle is connected to the process.

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		Proposed change (if any): Consistency of terms on the level of detail to the description of the equipment.	
161	1	Comment: Only critical process parameters should be given in order to avoid unnecessary variations. Proposed change (if any): Steps in the process should have the necessary detail in terms of critical process parameters along with their target values or ranges (general reference to “typically” set points is not acceptable for critical process parameter).	Comment not accepted. It is not agreed that only critical parameters should be part of manufacturing process description.
162-167	1	Comment: Parameters that have to be controlled or monitored during any unit operation to ensure process output and final product are of the intended quality, are considered critical parameters (i.e. having impact on CQA). The non-critical parameters and the rationale for considering those as non-critical should be described in section 3.2.P.2. The critical process parameters should be described in 3.2.P3. Proposed change (if any): Please delete sentences: All parameters that have been demonstrated during development as needing to be controlled or monitored during each unit operation, to ensure that the output from a processing step and also that the final product is ultimately of the intended quality need to be described.	Comment not accepted. It is not agreed that only critical parameters should be part of manufacturing process description.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
162-166	2	Comment: AZ considers this sentence to blur the lines between critical and non-critical process parameters. The conclusion of the sentence *"..the final product is ultimately of the intended quality need to be described."* Is considered by AZ to represent the definition of a critical process parameter. **Proposed change:** Please consider providing a definition for a non-critical process parameter. Also, if it is the expectation of the EMA to include non-critical process parameters in the manufacturing process description please explain expectations on handling these for compliance or as post approval changes.	Comment noted. Expectations on handling of non-critical process parameters post-approval will not be covered by this guideline.
166	4	Comment: The text states "details of non-CPPs should also be included at an appropriate level of detail to give a basic description…". What needs to be clear is what are the change management expectation for this information. Proposed change (if any): Please reconsider and re-clarify this important matter. For example: "Details of non-critical process parameters should also be included **for information** and at an appropriate level of detail to at least give a standard/basic description of relevant steps." Please refer to earlier comments on alignment with ICHQ12 considerations.	Point acknowledged. ICH Q12 will not be in contradiction with the proposed wording in this guideline.
166	4	This guidance as written is presupposing that CPPs are identified in all cases, which contradicts the examples in the annex. *The guidance provided in reference 4 (EMA/CHMP/CVMP/QWP/BWP/70278/2012 Annex I)*	Comment noted. Changes in the text of the guideline and in the Annex have been introduced to acknowledge that, while it is always expected that critical steps of the manufacturing process are identified, criticality of the process parameters is not always investigated in a systematic way.

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		states that the application should include: *"a summary of the critical processing steps <u>or</u> critical process parameters"* Please clarify this important point in the text.	
163-166, 168-169 & Annex example	7	Comment: The paragraph around line 163 and 166 refers to critical process parameters and non-critical process parameters for all manufacturing processes whilst Annex example only identifies CPP/non-CPP for the 'QbD application' and not for 'traditional application'. The paragraph should be amended to be consistent with the Annex. Proposed change (if any): As stated.	Comment noted. The text of the guideline and in the Annex have been changed to acknowledge that the comment; while it is always expected that critical steps of the manufacturing process are identified, criticality of the process parameters is not always investigated in a systematic way.
166-167	1	Comment: Non-critical process parameters should be given only in exceptional cases in order to avoid unnecessary variations. Proposed change (if any): Details of non-critical process parameters may also be included in rare cases at an appropriate level of detail to at least give a standard/basic description of relevant steps.	Comment not accepted. It is not agreed that only critical parameters should be part of manufacturing process description.
166-167 (and 363 accordingly)	3	**Comment and proposed change:** BPI suggests deleting "Details of non-critical process parameters should also be included at an appropriate level of detail to at least give a standard/basic description of	Comment noted. The whole paragraph has been rephrased to clarify the regulatory expectations.

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		relevant steps." and replacing it with "Non-critical process parameters should be included at the level of standard/basic description of relevant steps." **Rationale:** This proposed requirement is redundant since a more detailed information is matter of GMP	
166-167	5	Comment: The level of detail included within the registered process for non-critical steps should be minimal and generic, otherwise this detail would be a further cause for variations Proposed change (if any): Standard/basic description of non-critical process steps/parameters should be included.	Comment noted. The whole paragraph has been rephrased to clarify the regulatory expectations.
170	2	Comment: AZ does not understand the necessity of this section as at present it is confusing. The use of wording such as *"essentially"* can offer scope for misinterpretation and a potential compliance challenge for Pharma and the EMA. Also, the inclusion of *'wet/dry granulation'* in the final sentence of the 'Liquid dosage forms' section is confusing. **Proposed change:** Overall, this sections purpose is not clear and as a whole is considered not to add great value in addition to previous content of the guideline.	Comment noted. Text has been reworded for clarity.
170	4	Comment:	Comment accepted. The manufacturer/manufacturing site

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		The concept of technical adaptations is positive in recognising flexibility for more than one manufacturer or manufacturing site and associated different equipment. However this section would benefit from greater clarity to aid interpretation. Specifically, it would be helpful to confirm that introducing technical adaptations are equally acceptable within a manufacturer/manufacturing site given appropriate justification and post approval action, if that is the intention. Please add text: *technical adaptations are equally acceptable within a manufacturer/manufacturing site given appropriate justification*	has been added into the guideline for better clarity.
170-177 304	5	It is acknowledged in section “Technical adaptions in the manufacturing process” that “depending on equipment availability, different pieces of equipment could be used”. This should be reflected in the example (line 304). Moreover, it might be feasible to define parameters which are fixed for the manufacturing of the product (e.g. process step) and which could only be changed by a respective variation for change in manufacturing process (B.II.b.3) and other parameters (e.g. capacity) which could be amended as a consequential change with variation type B.II.b.1. Proposed change (if any):	Comment noted. However, it is not the intention of the example to reflect the “technical adaptations in the manufacturing process” section. Types of variations are not discussed in the guideline.
178	4	Comment: There are so many product types and manufacturing processes that we are not sure that	Comment not accepted. Examples to be kept.

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		giving lists of different equipment that can be used for some products is useful. Proposed change (if any): We recommend this information be omitted.	
187	5	Comment: It is not clear where this paragraph ends (line 189 or 194 or 204 or 209?) Proposed change (if any):	Comment noted. The text has been revised for clarity.
188	1	Comment: It is not mandatory to use only stainless steel tanks for the preparation of solutions. It should be specified that the material mentioned serves as an example. Proposed change (if any): “Preparation of solutions can be performed **e.g.** in simple stainless steel tanks equipped with …”	Comment accepted. Text has been revised as proposed.
190	4	Formatting issue: this text is no longer part of the explanation for liquid dosage forms. Can formatting be adjusted to make clear that this is no longer part of the Liquid Dosage discussion?	Comment noted. The text has been revised for clarity.
195	10	Comment: Editorial (avoid repetition). Proposed change (if any): Where relevant, the justified technical adaptations in various ~~manufacturing~~ steps in the manufacturing process	Comment accepted. Text has been revised as proposed.
195-204	1	Comment: The term “technical adaptation” should be defined in more details, since e.g. the use of different equipment of e.g. different size or different brand, but having the	Comment not accepted. The proposed definition is not endorsed.

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		same operating principle of a non-critical operating unit, should not be considered as a technical adaptation. A technical adaptation should only relate to different operating principles (e.g. tray dryer vs. fluid bed dryer) or different equipment types if the operation unit is considered critical. Proposed change (if any): A technical adaptation only relates to different operating principles (e.g. tray dryer vs. fluid bed dryer) or different equipment types if the operation unit is considered critical.	
195-204	3	*Where relevant, the justified technical adaptations in various manufacturing steps in the manufacturing process of one or more manufacturers and corresponding in-process controls should also be transparently shown in separate flow-charts, which, if applicable, should also include all adaptations. On presentation of separate flow-charts in a dossier the different manufacturing steps should be listed and the adaptations should be compared to each other by the applicant. The applicant should justify that adaptation, on the basis of using different equipment, do not have any significant influence on the drug product quality and this should be supported by data. The in-process controls and corresponding acceptance limits should also be described, when relevant.* ***Where any differences are proposed at different manufacturing sites, the information should always be presented in the same module 3***	Comment not accepted. The practice described by stakeholder is not acceptable; only one Module 3.2.P can be used for one product.

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		section document, but if required differentiated based upon the actual manufacturing site. Currently, the manufacturing processes at different manufacturing sites are usually presented in separate sections 3.2.P.3.3 as there are separate modules 3.2.P for each manufacturing site. This proceeding facilitates the addition or deletion of single manufacturing sites (as entire 3.2.P module) to or from the registration documentation. Furthermore, the comparison of differences between the manufacturing sites is not considered relevant for the assessment since the manufacturing process is fully validated for each manufacturing site. The validation results are presented for each site in separate sections 3.2.P.3.5 within their own 3.2.P modules. Irrespective of differences in manufacturing processes, the final drug product is characterised by one release and one shelf-life specification.	
195-204	4	This paragraph, as written, appears to be more applicable to P2.3 Manufacturing Process Development.	Comment not accepted. This information provides the details of what it is expected in section 3.2.P.3. of CTD Module 3.
203-204	4	Some applicants may have separate Module 3 documents for different sites. The text as written could imply that a consolidated Module 3 document is required if drug product is manufactured at multiple sites and they would not accept separate sections by site? There are many occasions where alternate sites use unique	Comment noted but no corrections considered necessary.

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		equipment and have equipment-specific controls. Therefore, it makes more sense to have a separate process descriptions. This would also simplify the lifecycle management of the documents for post-approval changes. Please clarify.	
205	3	**Comment:** The guideline points out that truly alternative manufacturing process which use different principles and may or may not lead to differences in the in-process control and/or drug product quality are not acceptable. BPI wants to point out that even when the manufacturing principle is the same, different IPCs can be used by different manufacturers. **Proposed change (if any):** BPI is of the opinion that the guideline should address this issue more precisely.	Comment noted but no corrections considered necessary.
205	10	Comment: Unclear wording. What is a "truly" alternative manufacturing process? Suggestion to delete the word. Proposed change (if any): … ~~truly~~ alternative manufacturing processes, which use different principles …	Comment accepted. The text is revised as proposed.
Lines 205-208	4	Recommended change: "In contrast to technical adaptations as described above, truly alternative manufacturing processes, which use different principles and may or may not lead to differences in the in-process control and/or drug product quality are not acceptable (e.g. using different sterilisation procedures – terminal	Comment not accepted. The techniques that lead to different properties of finished product or the use of sub optimal techniques would not be accepted in one dossier.

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		sterilisation of end product vs. aseptic manufacture using sterile filtration – possibly to reflect the use of different containers with different heat resistance properties; wet granulation vs. dry granulation) **unless demonstrated by comparability or an appropriate product quality assessment**." Recommending additional clarification of when changes would be acceptable.	
205 - 209	4	Comment: This paragraph should not be generic but refer solely to liquid dosage forms. Proposed change (if any): Move paragraph after line 175.	Comment noted. Order of the paragraphs has been changed.
205-209	12	Comments: It is not entirely clear what exactly is meant as "truly alternative manufacturing process"; if processes that use different principles, this is recommended to be made more clear. Moreover, it is noted that differences in the in-process control should not be recognised as such that define essentially different manufacturing processes (such differences in IPC may result from different manufacturing equipment used at particular manufacturing sites, even if of the same type). Proposed change: In contrast to technical adaptations as described above, ~~truly alternative~~ manufacturing processes, which use essentially different principles and/or may ~~or may not~~ lead to significant differences in the ~~in-process control and/or~~ drug product quality are not acceptable (e.g. using different sterilisation procedures – terminal	Proposed change not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sterilisation of end product vs. aseptic manufacture using sterile filtration – possibly to reflect the use of different containers with different heat resistance properties; wet granulation vs. dry granulation).	
207	6	Comment: Should be acceptable with prior approval; equivalent product can be made in many cases with a different process and in process control strategy.	Comment not accepted.
209	1	Comment: Wet granulation and dry granulation do not match with the paragraph header. Proposed change (if any): Please delete “wet granulation vs. dry granulation”.	Comment noted. The section and relevant text has been reworded.
211-213	3	**Comment and proposed change:** BPI suggests to change the wording as follows: “Where relevant, ~~All~~ critical steps and intermediates isolated during the manufacture of the finished drug product should be listed in this section including.” **Rationale:** This proposed requirement is not applicable in general. BPI suggests deleting the subsequent wording “…details about the sampling strategy” **Rationale:** This proposed requirement is redundant since it is matter of GMP.	Comment partly accepted: “…details about the sampling strategy” has been deleted.
211	4	Comment: This Section is titled “critical steps” but the text in lines 213-216 is regarding CPPs.	Comment noted; however, no change is deemed necessary on this aspect.

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		Proposed change: Suggest that the link between “critical steps” and CPPs is explained more clearly. See also our comment with respect to reference 4	
212	4	Comment: Sampling strategy is was not a previous requirement. Therefore it is suggested to remove this GMP information, unless somehow critical to the control strategy	Comment accepted. However, it is noted that in the control strategy the frequency and sampling can have important role. “…details about the sampling strategy” has been deleted.
211; 220-222	4	Comment: Definition of the term “intermediate” according to the EU GMP Guideline is “Partly processed material which must undergo further manufacturing steps before it becomes a bulk product”. Definition of the term bulk according to the EU GMP Guideline is “A bulk is any product which has completed all processing steps up to, but not including, final packaging.” The definitions provided in this document seem to be in contradiction to the EU GMP guidelines. Terms should be consistently defined within EU regulations and guidance documents.	Comment accepted. The text has been revised to be in accordance with EudraLex volume 4. Definitions (GMP glossary) for intermediate product and bulk product have been included.
211-212	5	Comment: The term “sampling strategy” should be defined in more detailed. Sampling is part of GMP requirements and therefore not in scope of this guideline. Proposed change (if any):	Comment accepted. “…details about the sampling strategy” has been deleted.
212-213	9	Comment: Please consider to change the wording from …strategy to …points. Proposed change (if any): …including details about the sampling points, applied	Comment noted. “…details about the sampling strategy” has been deleted.

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		test methods and acceptance criteria.	
213-218	7	Comment: Contrary to line 33 which states this guideline does not introduce new requirements it does appear to do so. For example, lines 213 to 218 could be interpreted as requiring justification for the identification of PPs vs CPPs and link to experimental data and risk assessment which would be a new requirement for traditional development products (to which this guideline also applies as per scope section) and which does not align with Annex example. *Proposed change (if any):* Correct expectations, aligned with Annex example.	Comment noted. Text and Annex have been revised elsewhere for clarity.
219-227	4	Comment: Please clarify if hold time is intended to cover only hold time between steps, or also the processing time within the processing step. That is, is hold time defined from the end of one processing step to the start of the next processing step (end to start) or the end of one processing step to the end of the next processing step (end to end). Proposed change: 227: solution prior to filling granulates, uncoated tablets, etc. ***Hold time is the period of time from the end of one processing step to the start of the next processing step.***	Comment accepted. A definition for 'Hold time' has been provided.
219-236	4	Comment: Please clarify if bulk storage refers to the bulk drug	Comment noted. Terminology has been checked and revised.

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		product (prior to packaging) in addition to material isolated in-process, and if the expectation for stating hold times and reasons for prolonged storage for bulk applies to bulk drug product (prior to packaging).	
219-257	10	Comment: Include a definition for "bulk product" that explains the use in both lines 83 and lines 223 or provide an alternate term and definition where the meaning is different. Proposed Change: The definition from Eudralex Volume 4 seems applicable for the use in line 83 but perhaps a modified definition is needed for the use in lines 223 – 225 such as: Bulk product: A product which has complete all processing stages up to but not including **final formulation** or final packaging.	Comment noted. Terminology has been checked and revised.
219-252	2	Comment: Please confirm whether stability and product shelf life should be determined based on the additive effect of each hold. Please clarify if there is an expectation that shelf life be determined based on product manufactured at the greatest extent of each hold time. AZ are concerned that if supply chain requirements were to change, and a product (incl. intermediates e.g. granule) demonstrated a high degree of stability, that asset, manufacturing and supply flexibility will be decreased if Pharma were expected to file post approval changes for any increase in hold time post initial filing.	Comment noted. No correction in the text needed.
220	4	Comment: The term “sequential processing steps” needs further explanation. Proposed change (if any): We propose to use the term ”unit operation” for a single or a subset of	Comment accepted. In the text ‘sequential processing steps’ has been replaced with ‘unit operations’.

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		processing steps where the output (intermediate or bulk) is isolated and held, possibly after some confirmatory testing of quality.	
228	4	Comment: This paragraph is not clear regarding when bulk storage conditions need to be registered. Are bulk storage conditions required to be registered ONLY if the time is more than 30 days for solid oral dosage forms and 24 hours for sterile products? Or is ANY storage time required to be registered? Proposed change (if any): Provide additional clarification for when bulk storage conditions need to be registered. Please clarify that hold times need to be stated in the case of prolonged storage, not for every processing step.	Comment noted. The text of this chapter has been clarified. Definition of bulk product and intermediate product has been added. Information about holding time has been revised.
228/229	5	Comment: The term “storage” should be defined more clearly. Otherwise this requirement would be mandatory for every intermediate (e.g. pre-mix of API with excipient, wet mass after granulation, dry granulates, dry granules after sieving, pre-blend, lubricated blend, uncoated tablets, film-coated tablets) Proposed change (if any): Include a clear definition and link it to a holding time of e.g. 24 h for non-sterile products and 8 h for sterile products. Only if this holding time is exceeded the requirements should become mandatory.	Comment noted. See above.
228	6	Comment: No need to state if the bulk product is to	Comment not accepted. Mentioning prior approval,

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		be stored and under what conditions because it is acceptable with prior approval that equivalent product can be made in many cases with a different process and in process control strategy.	equivalent product, and different process control strategy as a reason for not stating storage of bulk product is not acceptable.
228-230	10	Comment: PDA is concerned that the example provided will be viewed as an implied requirement to challenge the maximum hold time during process validation runs. In PDA's opinion that would be too prescriptive and not aligned with current PV thinking. Companies should be able to provide whatever evidence and data is appropriate to support their specific product and proposed process hold times for evaluation by the regulators to judge whether that evidence adequately supports the claim. Proposed Change: *"… maximum holding times of bulk product should be stated and appropriately supported by data ~~(e.g. challenging the maximum hold time in process validation studies or by providing dedicated stability studies for the bulk storage~~).*	Comment not accepted. The statement in brackets is only a non-exhaustive example.
228-233	12	Comment: The requirements for bulk storage would be expected to be compliant with those which are already present on the EMA website (Q&A on quality, part 2). For example, in the Q&A it is stated that "The maximum storage interval for the bulk product should be declared in the marketing-authorisation dossier, or alternatively, the maximum batch manufacturing time from start of product manufacture to completion of packaging in the final primary container for marketing". In the draft guideline the declaration of maximum batch manufacturing is given as an additional requirement (not as an alternative).	Comment accepted. Proposed change accepted.

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		Proposed change (if any): "It should be stated whether any bulk product is to be stored and if so, under which conditions. The level of information to be provided in the documentation is dependent on the nature of the bulk product. Where relevant, the maximum holding times of bulk product or – alternatively – the maximum batch manufacturing time from start of product manufacture to completion of packaging in the final primary container for marketing should be stated and appropriately supported by data (e.g. challenging the maximum hold time in process validation studies or by providing dedicated stability studies for the bulk storage). ~~In addition, where relevant, the maximum processing times of both individual and a combination of processing steps (e.g. from the start of manufacture to packaging for aseptic processing) should be appropriately supported.~~	
229	5	Comment : In our opinion, Intermediate holding time should be provided only when there is a need for the manufacturing process to exceed 30 days (starting with weighing of the substances) or when special storage conditions are required (e.g. low temperature, low humidity levels).	Comment noted. The statement is not in contradiction to proposed text.
233-234	2	Comment: AZ recommends removal of the reference to GMP to maintain focus on quality and compliance. **Proposed change:** Suggest re-wording to ***"The reasons for any prolonged storage / processing times should be stated and justified."***	Comment noted. Reference to GMP to be kept.

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233-234	12	Comment: It is not entirely clear what (additional) data are required for 'prolonged' storage/processing times (in comparison with data required 'not-prolonged' times). Moreover, it is not clear how reasons for such prolonged times should "be consistent with GMP".	Comment noted. The text of guideline has been slightly revised to better explain the issue. In case stability data are needed to cover prolonged storage, the same requirements as any other stability study are applied, unless otherwise justified. The consistency with GMP implies that the need for prolonged storage is a necessary part of manufacturing process and not an unexpected deviation that has occurred.
235-236	5	Comment: The EGA would appreciate further guidance that relates to other galenical forms such as creams, gels, eye/ear drops etc.	Comment noted. However, it is not the intention of guideline to provide detailed information on how each dosage form should be treated while stored as bulk.
235-236	6	Comment: These two times are baseless. "Prolonged" is a function of what can and does change and this is case by case.	Comment noted. No change proposed.
237	2	Comment: Please confirm whether it is a new commitment to *specify "…holding time should be provided (on at least 2 pilot scale batches."* AZ considers the requirement for 2 batches minimum to be a constraint on Pharma. Please confirm whether it is acceptable for Pharma to perform sufficient hold time studies based on available stability knowledge of the intermediate and product. With appropriate scientific rationale and justification (e.g. if one batch is used).	Comment noted. No change to the text.
237	4	Overall, provision of data should be based on risk, and only applicable to cases of prolonged storage which is not currently clear in the text as worded. Such data should scientifically justify the storage period, and not mandate information from 2 pilot scale batches as stated.	Comment not accepted. The requirement on the provision of stability data from three batches, with two of them at least pilot scale, is stated in ICH Topic Q 1 A (R2) and has been implemented for many years. The justified risk based approach can be used in every case.

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237-238	1	Comment: One batch should suffice, bracketing should be possible. Proposed change (if any): Where relevant, stability data to support the holding time should be provided (on at least one pilot scale batch).	Comment not accepted. The requirement on the provision of stability data from three batches, with two of them at least pilot scale, is stated in ICH Topic Q 1 A (R2) and has been implemented for many years. The justified risk based approach can be used in every case.
237-238	5	Comment: Stability data from one pilot-scale batch of the bulk product is evident of satisfactory quality of the product. Moreover, the FDA and Health Canada require data from one pilot-scale batch of the bulk product. In the interests of regulatory harmonization across major regulatory markets and single development program the guideline should be amended. In case of more strengths, we propose to include Risk based approach in case of more strength (worst case tested in the stability study). Proposed change (if any): Where relevant, stability data to support the holding time should be provided (on at least one pilot scale batch). *In case of more strengths, stability data should be provided for the most critical strength based on the risk based approach.*	Comment not accepted. The requirement on the provision of stability data from three batches, with two of them at least pilot scale, is stated in ICH Topic Q 1 A (R2) and has been implemented for many years. The justified risk based approach can be used in every case.
241-245	12	Comment: As for calculation of the batch shelf-life it is recommended mentioning specific provisions applicable to some groups of medicinal products, in particular vaccines. According to the Ph.Eur. monograph “Vaccines	Comment noted. Text not changed.

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		for human use" (0153), the expiry date is normally calculated from the beginning of the assay or from the beginning of the first assay for a combined vaccine.	
246	1	Comment: Transportation of bulk is subject to GTP/GMP and therefore should not be included in CTD Module 3. Proposed change (if any):	Comment noted. Text of the paragraph has been reworded. Transportation of bulk is kept in the guideline; reference to GDP has been deleted.
246-249	2	Comment: AZ does not understand the need for what appears to be a justification of a supply chain, which could change based on market demand. Pharma are already committed to the *"Note for guidance on the start of shelf life of the finished dosage form"*. Also, the reference to *'short'* or *'longer excursions'* is understood by AZ to refer to one off excursions, if this is the case please confirm if these should not be handled as such with relevant stability data for that specific event under GMP. **Proposed change:** AZ recommends the removal of this paragraph.	See above.
246-249	3	**Comment and proposed change:** *Transportation of bulk between manufacturing sites should be explained and justified. The principles of the guideline on Good Distribution Practice (ref 10) and guidance given in GMP Annex 15 on transport should be taken into consideration. The impact of short or longer excursions outside of the original storage*	Comment on GDP accepted. However, text related to the transportation has been kept (see above). Reference to GDP has been deleted.

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		conditions should be discussed and, where necessary, supported by accelerated stability data. GDP issues are not considered to be relevant information which should be included into the CTD module 3 of the registration dossier.	
246-249	4	Transport of bulk product between manufacturing sites is an inspectable GMP aspect and should not be included in the registration dossier. The impact of short or longer excursions outside of the original transportation and storage conditions is suitably addressed by the verification of the transportation, as described in EU-GMP Annex 15 by performing a risk assessment to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored. Proposal: delete sentence as emphasized below "TRANSPORTATION OF BULK BETWEEN MANUFACTURING SITES SHOULD BE EXPLAINED AND JUSTIFIED"	See above.
246-249	5	Comment: The guideline states that “Transportation of bulk between manufacturing sites should be explained and justified”. This sentence requires clarification. Also more guidance on what type of information is expected and on acceptance criteria would be welcomed. The industry does not see added value in explaining and justifying transportation of bulk between manufacturing and packaging sites as transportation of bulk between sites	See above.

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		is e.g. done because of flexibility of packaging for (smaller) European countries. Compliance with GDP principles and GMP Annex 15 fall under the responsibility of GDP and GMP, respectively and are outside the scope of this guideline. Also the impact assessment of excursions are elements of GMP and should be omitted from this guideline. Proposed change (if any): ~~Transportation of bulk between manufacturing sites should be explained and justified. The principles of the guideline on Good Distribution Practice (ref 10) and guidance given in GMP Annex 15 on transport should be taken into consideration. The impact of short or longer excursions outside of the original storage conditions should be discussed and, where necessary, supported by accelerated stability data.~~	
246	6	Comment: The details of this may change often; principles should be defined in the guideline but details should not be filed.	Comment noted. However, it is considered sufficiently described. No change has been implemented.
249	6	Comment: Sometimes there is real data vs. a formal accelerated model. Proposed change (if any): add bolded text: “supported by accelerated or real time data stability data”	Comment noted. The text has been revised to include “or real time data”.
246-252	1	Comment: Transport of bulk products between manufacturing sites	Comment not accepted. The impact of prolonged excursions from the proposed storage conditions should be discussed in

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		and control specification are inspectable GMP aspects and should not be included in the registration dossier. Proposed change (if any): …The materials of the bulk container closure system should be described in the dossier.	the CTD Module 3 dossier.
250	1	Comment: Only material that is used for Bulk storage should be concerned. Proposed change (if any): The suitability of the proposed container closure system intended for bulk storage should be justified.	Comment accepted.
250	3	**Comment** The suitability of the proposed bulk container should be justified. It is questionable to BPI companies if this information should be filed in 3.2.P.3 or 3.2.P.7 **Proposed change (if any):** According to BPIs opinion, the information should be filed in 3.2.P.7 and stability data should be filed in 3.2.P.8. In Chapter 3.2.P.3.4 a reference should be made to these chapters.	Comment noted; the mention “in relevant parts of the dossier” has been included in the text.
250-252	3	**Comment and proposed change:** BPI suggests changing the wording as follows “Primary packaging material used for bulk storage ~~suitability of the proposed bulk container closure system~~ should be described in the dossier ~~justified~~.	Comment not accepted. It is common practice to provide information about packaging materials used for storage.

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		The type and level of information required will depend on the nature of the bulk product. ~~The materials of the bulk container closure system should be described in the dossier and its control specification stated.~~" **Rationale:** This proposed requirement as inclusion of more details is not appropriate, in principle, but will cause additional work /variations in future.	
251-252	4	Proposal: delete half sentence as emphasized below "The materials of the bulk container closure system should be described in the dossier AND ITS CONTROL SPECIFICATION STATED." Rationale: The information is an inspectable GMP aspect, and should not be included in the registration dossier.	Comment not accepted. It is common practice to provide information about packaging materials used for storage. Reference is made to current Q&A on stability issues of pharmaceutical bulk products
251-2	4	Comment: Contrary to what is stated in line 33, expectations for the bulk container closure system and its control specification are additional requirements. Is this detail required only for prolonged holding times? Proposed change (if any): Please clarify	See above.
251 - 252	4	Comment: It should be specified, in which dossier section bulk container closure should be presented.	Comment noted; however, no precise location is provided in this guideline.
251-252	5	Comment: The Notice to Applicant Volume 2B does not require specifications to be submitted for non-functional secondary packaging materials (for finished products). The current wording requires more detail for bulk packaging materials than those are in place for finished	Comment accepted. The proposed change has been included in the revised text.

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		product packaging, which is not considered necessary. Proposed change (if any): The materials of the bulk container closure system should be described in the dossier. The control specification for primary bulk packaging should be stated.	
253	4	It would help if this subsection briefly outlines what information from previous subsections should be included here. Alternatively, the other subsections could clearly indicate that requested information should be presented in P.3.5. For example, the hold time qualification data requested in lines 237-240 could be presented in P.3.5.	Comment not accepted. All relevant information is mentioned in the process validation guideline. It is not agreed that the information on bulk stability, mentioned on lines 237-240, should necessarily be part of process validation, this information could also be included in 3.2. P.8 Stability.
254-255	2	Comment: AZ recommends that the wording here is maintained at a high level, e.g. Details on expected contribution are described in the Process Validation Guideline (ref 4). Alternatively please clarify what documentation requirements or filing content is expected to be submitted or commitments required at time of filing. It is understood that process validation must be carried out prior to manufacture for the market (EMA Guideline on process validation for finished products), however validation may be carried out after filing to maximize efficient use of input materials and manufacturing resources.	Comment partly accepted. Reference is made to the Process Validation guideline.
300+ ANNEX	4	The Annex example of a manufacturing process description is potentially unhelpful. See earlier	Comment not accepted. The Annex is an important part of this guideline; however, the text and examples have been

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		comments.	revised to better suit the purpose.
300-305	9	Comment: *Please be informed that if a greater understanding of the product and the manufacturing process (ICH Q8, EMA/CHMP/ICH/167068/2004) can be presented than a reduced level of detail may be justified (f.e. only "vertical impeller geometry")* Proposed change (if any): Insert in section after line 358: *A reduced level of detail may be justified if a greater understanding of the product and the manufacturing process can be presented acc. to ICH Q8 (EMA/CHMP/ICH/167068/2004).*	Comment not accepted. The information about the manufacturing process has to be submitted in sufficient detail to be assessed and understood whatever the approach taken for the pharmaceutical development. However, depending upon the level of process understanding gained during development and also the control strategy, the way the information is presented may be slightly different and the manufacturing process will reflect any justified and supported flexibilities when an enhanced development approach has been followed *e.g.* wide ranges established on a multivariate basis.
305-307	2	Comment: AZ considers the level of detail expected by the EMA provided in the file (e.g. Equipment type) to be restrictive and AZ has a concern that this could increase post approval change burden for pharma and the EMA, i.e. if reacting to market demand requires use of different equipment scales. This also is considered to contravene the text *in "Technical adaptions in the manufacturing process"*. We suggest that instead Pharma should provide a justification in the file of different equipment types under the same operating principal across a justified or proven range of scales.	Comment noted. Details about equipment type in the Annex have been revised. This issue is also covered in other part of the guideline.
307	2	Comment: AZ recommends that it is clarified (if it is the EMAs intention) that only parameters considered or demonstrated to be critical to quality should be provided.	Comment noted. However, it is not the intention to state that only parameters critical to quality of product should be mentioned. This issue is also covered in other part of the guideline.
Annex	3	**Comment:**	Comment not accepted. The Annex is important part of this guideline; however the text and examples have been revised

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		In the Annex of the Guideline is an example for filing a manufacturing process. The example should be deleted and the description of the manufacturing process should be filed according to the individual manufacturing process that is robust and consistent and has been validated accordingly.	to better suit the purpose.
307-324	1	Comment: Our understanding is that the list is not only non-exhaustive but also not mandatory, as only those parameters identified as critical parameters should be considered. Proposed change (if any): Non exhaustive list of process parameters which should be considered if they are identified as critical process parameters for the manufacturing process:	Comment partly accepted. Clarification is provided in the text of the Annex.
307 & 327	4	Comment: The list of parameters considered and list of parameters investigated will be presented in P.2 Pharmaceutical Development and shouldn't appear in the manufacturing process description section.	Comment noted. Clarification is provided.
307 & 327	7	Comment: Annex example incorrectly implies that lists of parameters considered and investigated during development would be included in the manufacturing process description rather than described as part of manufacturing process development. This should be corrected as well as emphasising that the parameters listed are for guidance purposes and not mandated.	Comment noted. Clarification is provided.

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307- 335	4	The example suggests that justification of the control strategy needs to be repeated in P.3.3. This appears redundant. The same information is also included in the parameter tables in the example, which seems a more logical presentation as the current lists of parameters do not contain the justification for the selection of parameters.	Comment noted. Clarification is provided.
337-350	7	Does this same narrative description apply to both traditional and QbD applications? Would some extent of differentiation be expected based on the level of scientific knowledge and understanding?	The same narrative description applies to both traditional and QbD applications. Clarification has been provided and text has been slightly revised. Differentiation has been made at the level of process parameters settings (tables).
342 and 351 (equally applies 342 and 351)	4	Comment: Not clear what target fill volume expressed as 30%w/v (180kg) means? Assuming that 180kg is the blend charge in a 600L vessel, this gives 30%w/v but why additionally express in this manner and what is the benefit?	Comment accepted. Text is revised accordingly.
351	7	Comment: There is no indication about criticality of parameters for the traditional application example. This does not align with elsewhere in the guideline text, where criticality is implied for process parameters. Proposed change (if any): Clarification in the guideline text around the need to describe critical steps and/or critical process parameters for traditional vs QbD applications.	Comment noted. The guideline text has been revised to acknowledge that while it is always expected that critical steps of the manufacturing process are identified; criticality of the process parameters is not always investigated in a systematic way.
351, 355	8	Comment: The wording with respect to numerical values for	Comment noted. Tables for process parameters settings in the annex have been revised accordingly. Differentiation

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		process operating conditions (target values and ranges) may cause authorities to request a level of details that would lead to avoidable variation applications while not adding safety to the pharmaceutical product. The examples provided in lines 351/355 evoke the impression that any kind of parameter ranges may in future only be acceptable if supported by QbD. Due to common technical limitations of industrial manufacturing processes and measuring systems, parameters like temperatures, volumes, weights, reaction times, flow rates etc. will *always vary* to a certain degree during actual production. Setting explicitly single “target values” instead of ranges would in numerous cases not be reasonable neither from technical point of view nor from common scientific and process understanding. Additionally, the guideline text does not clarify to which extent one may deviate from a target value without facing regulatory non-compliance issues and creating the need for a variation request. Proposed change: It should be made clear that for reasons of common production practice, technical limitations and scientific process understanding, it is reasonable to indicate ranges or upper/lower limits for certain process parameters. It should be explicitly mentioned that this does not only apply for QbD applications. Line 351: the third column heading in the table “Description of the manufacturing process (traditional	between traditional and enhanced (QbD) developments in terms of ranges (extent and justification) is made in the tables. The idea of normal operating range has been introduced in the text of the guideline to cover the common and unintentional variability of the process and measuring systems.

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		application)" should be identical to the one in the table "Description of the manufacturing process (QbD application)" and read "Target value or range". Like is it would be made clear that in certain cases also in non-QbD applications reasonable ranges may be indicated for selected parameters for the reasons mentioned above.	
351	9	Comment: *The guideline presents a traditional application and a QbD application.* *Please give some additional guidance for a traditional application with respect to the permitted variance around the target value.* *Secondly, please provide some guidance whether Proven Acceptable Ranges (PAR) may be applied for traditional applications since that would support a scientific basis for the variance around the target value.*	See above.
351&355	10	Comment: Please consider a single example that includes criticality. Previous documents such as *Guideline on process validation for finished products and data to be provided in regulatory submissions* of 27 Feb 2014 suggests that process validation address critical steps (and presumably critical parameters) of the manufacturing operation. There is no provision in any other document to ignore criticality. (see also comment to lines 154-156)	Comment noted. The guideline text has been revised to acknowledge that while it is always expected that critical steps of the manufacturing process are identified; criticality of the process parameters is not always investigated in a systematic way. *To a certain extent*, criticality is addressed when switching from the "early development list" to the "final development" list of process parameters.
355	4	**Comment** The term "QbD application" has a wide range of meanings since elements of QbD can be incorporated to different extents in different parts of the CTD. .	Comment acknowledged. QbD has been replaced by enhanced development approach.
355-6 and	4	Clarification on use of terms – 'target values and range'	Comment noted. The terminology has been aligned with the

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363		– see earlier comment line 122 and also our position with respect to the Agency's draft Q&A EMA/689005/2017 on manufacturing process descriptions.	draft Q&A EMA/689005/2017 on manufacturing process descriptions (not yet published) and with the amended text in the guideline. Clarification on use of these terms is provided by the examples in the tables for process parameters settings.
359	4	. EFPIA highlights that the expectations for a traditional compared to a QbD application provided by the Annex are not clearly differentiated elsewhere in the text of the guideline Given that the criticality of operational parameters may not be fully established for older products that were not developed using a modern pharmaceutical development approach, it would be burdensome to transition a traditional application to a QbD application. Proposed change (if any): Clarify in the guideline that hen changes to an approved application are required, continuation with a traditional approach or updating the application to a QbD approach should be at the applicant's discretion.	Comment acknowledged. Changes in the text of the guideline and in the Annex have been introduced to acknowledge that while it is always expected that critical steps of the manufacturing process are identified, criticality of the process parameters is not always investigated in a systematic way. An introductive paragraph has been added to the Annex to highlight the non-mandatory character of the proposed example.
361&362	7	Comment: Unclear on expectations differentiating 'operating principle' and 'equipment type' (either in the guideline lines 157-158 or exemplified here in Annex).	Comment noted. "Operating principle" in the Annex has been replaced by "manufacturing process principle". Text of guideline has been aligned.
363	1	Comment: Only the critical process parameters should be described in order to avoid unnecessary variations. Proposed change (if any): Critical process parameters described (with target values or ranges) leading to a comprehensive	Comment not accepted. The information on the manufacturing process has to be submitted in sufficient detail to be assessed and understood. It is not EMA intention to mention only parameters critical to the quality of product. This has been further clarified in the text of the Annex. This issue has also been covered in other part of the guideline.

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		description of the unit operation.	
363	7	Comment: Unclear if note on 'Critical and non-critical process parameters described (with target values or ranges)...' equally applies to a traditional application since this does not align with the apparent differentiation of expectations for traditional compared to QbD applications exemplified within the Annex example.	Comment acknowledged. The text of the note has been further clarified.
363-364	2	Comment: AZ would like to understand the EMAs expectation on whether non-critical process parameters need be included for both traditional and Design Space filings. Please clarify if the expectation is for non-critical process parameters to be included in the manufacturing description or in other parts of the filing. If non-critical parameters are included in the manufacturing process description, AZ would like to understand the EMA expectation on their handling as a compliance commitment/post approval change. **Proposed change:** AZ would also recommend providing a definition for non-critical process parameters under "Definitions" to maintain understanding between Pharma and the EMA.	Comment noted. Changes in the text of the guideline and in the Annex have been introduced to acknowledge that, while it is always expected that critical steps of the manufacturing process are identified, criticality of the process parameters is not always investigated in a systematic way. For applications, able to assign criticality to process parameters, it has been clarified that both critical and non-critical parameters are expected to be *included in the process description*. Expectations on post approval management will be covered by ICH Q12 guideline, which is currently under development.
365-379	7	Comment: What should be considered differently for the QbD application compared to the traditional application? Is scientific knowledge/justification and/or data equally acceptable or expected for both? Proposed change (if any):	Comment noted; however, this is not in the scope of this guideline. Justifications pertain to ICH Q8 (R2) guideline. Differences in terms of process description are covered by the examples of the Annex.

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		Clarity on differentiated expectations is required.	
376-379	2	Comment: AZ recommends that the purpose of the Annex sub section “to note:” is made clearer. Also, if this sub section is considered important to the content of a filing then AZ recommends that the guidance clearly reflects the EMA expectations presented in the Annex earlier in the main text of the guidance document, e.g. section 4.3, rather than a sub section of an Annex. To conclude, AZ found the Annex a challenge to follow, and request that rather than it being a mix of EMA points to consider, expectations and examples, that the Annex is presented in such a way that Pharma can easily comply with EMA expectations.	Comment noted; the main lessons from the Annex have been reflected in the text of the guideline. Overall, the annex has been amended to better suit the purpose.