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Ref : Guideline on Process Validation
EMA/CHMP/CVMP/QWP/70278/2012-Rev1
29 March 2012

To the EMA Quality Working Party (QWP):

PDA is pleased to provide comments on the revised EMA *Guideline on Process Validation*, released for consultation on 29 March. We recognize that the purpose of the Guideline is to describe information to be considered for submission in the dossier; and that it is not intended to give guidance on "how" to conduct validation in the industrial manufacturing environment.

Our comments were prepared by an international group of expert volunteers with experience in validation, regulatory affairs and GMP. The comments consist of 2 general comments and 14 specific technical comments related to sections of the guideline, which can be found below in the comment matrix.

If you have any questions, please contact me.

With very best regards,

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Attachment

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cc: S. Rönninger, S. Schniepp, H. Baseman, S. Bozzone, R. Levy, R. Dana, J. Miller

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<30 October 2012>

PDA Comments on, '*Guideline on Process Validation,*' (EMA/CHMP/CVMP/QWP/70278/2012 – Rev1 29 March 2012)

Comments from: PDA

Parenteral Drug Association (PDA): Represented by Dr. Georg Roessling (roessling@pda.org)

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General Comments:

PDA No.	Stakeholder # *(EMA)*	General comment (if any):	Outcome (if applicable) *(EMA)*
1		**Comment:** The Executive Summary of this guideline states, in part, *"...The guideline is brought into line with ICH Q8, Q9 and Q10 documents and the possibility to use continuous process verification... and clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality system as described by ICH Q8, Q9 and Q10."* PDA fully supports a revision of the guideline to meet those goals. However, we note that the definition of Process Validation in the guideline remains the same definition described in EU GMP Annex 15, Validation and Qualification. This definition dates from 2001 and reflects the understanding and conduct of process validation before the advent of the referenced harmonised ICH quality guidelines. **Recommendation:** For the above reason, and consistent with the goal of international harmonization of regulatory guidance, we suggest the EMA consider adoption of an updated definition of Process Validation which captures the benefits of ICH Q8, Q9, Q10. A starting point for consideration is the definition used by FDA in their revised process validation guidance published in January 2011 and which does capture the ICH concepts, to promote language consistency. We would like to also note that portions of the FDA definition are also used in the text of ICH Q11.	

2		**Comment:** The guidance mentions that information on process validation should be included in the dossier (e.g. Module 3) but does not describe which section should be used. For example, in the EU CTD information about process validation (drug product) can be provided in the following sections: - 3.2.P.2.3 Manufacturing Process Development; Feasibility of Continuous process verification strategy (line 167), Hybrid (line 186), production scale data (line 238) - 3.2.P.3.5 Process Validation and/or Evaluation - 3.2.R Process Validation Scheme for the Drug Product (EU regional part). **Recommendation:** We believe it will be helpful to both assessors and applicants if the guidelines for preparing eCTD submissions provide clear guidance on which section process validation data should be presented. Alternatively, the specific Process Validation guideline could be modified to give clear recommendations regarding which sections of the dossier are preferred for the placement of validation information.	

2. Specific Comments on Text:

PDA No	Line number(s). *(e.g. Lines 20-23)*	Stake # *(EMA)*	Comment and rationale; proposed changes	Outcome *(EMA)*
3	Section 1. Introduction Lines 56-58		**Comment:** This paragraph states, *"Process validation should not be viewed as a one-off event. A lifecycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production."* While this can be considered an accurate statement we feel it is more helpful to describe the activities and principles on which process validation studies are based (rather than a statement of what PV is not.). **Proposed change (if any):** For clarity we recommend to: -Delete the first sentence of this paragraph, "~~Process validation should not be viewed as a one-off event.~~" -Revise the 2nd sentence to read, "**Process validation incorporates** a lifecycle approach ~~should be applied~~ linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production."	
4	Section 2. Scope Lines 63-66		**Comment:** The Scope section includes the statement, *"The fundamental principles described in this document are applicable to biological products, however, these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance."* It is not clear how one should assess biological products on a case by case basis - what aspects of "complex nature and inherent variability" should be assessed? We have proposed some wording which leaves the guideline as applicable to biological products but recognizes the complexity of the biological substance. The words about 'case-by-case' and 'inherent variability' are not necessary and have been removed.	

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			Proposed change (if any): For clarity regarding the scope of the guideline, we propose revision of the above statement to read, "The fundamental principles described in this document are applicable to biological products, **but may require adaptation** ~~however, these should be considered on a case-by-case basis~~ in view of the ~~complex~~ nature ~~and inherent variability~~ of the biological substance."	
5	Section 4. General Considerations Lines 80-84		**Comment:** This sentence states, *"Process validation can be performed in a traditional way as described below; however there is also the possibility to implement continuous process verification if an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience*. A combination of process validation and continuous process verification may be employed." In addition to the above, we believe there may be a combination of approaches where the appropriate manufacturing technologies are available in the commercial manufacturing. **Proposed Change (If any):** We suggest additional language be added at the end of the last sentence and the paragraph should read, "Process validation can be performed in a traditional way as described below; however there is also the possibility to implement continuous process verification if an enhanced approach to development has been employed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience. A combination of process validation and continuous process verification may be employed **where appropriate manufacturing technologies are available to enable this approach**.	
6	Section 5.1. Traditional process validation Lines 92-94		**Comment:** The 2nd & 3rd sentences of this paragraph read as follows, *"It is recognised that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilised."* The 3rd sentence is confusing, e.g., what is the definition of a "valid" manufacturing process if it is not validated? Our expert group had	

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			several different interpretations of the intended meaning of this sentence and could not agree on the intent. **Proposed change (if any):** Change the sentence in line 92-93 and add 'full/complete' before process validation to improve clarity. Then we recommend deletion of the sentence in lines 93-94 as it is confusing, and not really necessary in the context of the remaining paragraph. The two sentences on lines 92-94, will then read, "It is recognised that, at the time of submission, **full/complete** process validation data may not always be available. ~~Nevertheless it is essential that valid manufacturing processes are always utilised~~."	
7	Section 5.1. Traditional process validation Lines 102 - 103		**Comment:** The last sentence of this section states, "*The competent authority may decide on limitations for a post approval increase of the batch size.*" The EU Guideline on the details of variations to the terms of marketing authorisations (currently under revision) defines conditions to be fulfilled and documentation to be supplied for any changes in the batch size of the drug product/ **Proposed change (if any):** Delete existing sentence in lines 102/103, and add new sentence as shown below. "~~The competent authority may decide on limitations for a post approval increase of the batch size.~~ As regards to any post approval changes to the batch size, reference is made to the respective EU Variations Regulation and related guidelines".	
8	Section 5.1. Traditional process validation Lines 115-127		**Comment:** These lines read: *"In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier, e.g. in those circumstances where the product is a biological / biotech product, where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale, or for specialised products such as certain modified release preparations (for medicinal products for human use, see the Note for guidance on quality of Modified release products; for those for*	

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			veterinary use, see the Note for guidance on the Quality of Modified Release Dosage Forms for Veterinary Use). Where non-standard sterilisation methods or aseptic processing are employed, data should be provided on a number of consecutive batches at production scale prior to approval. The number of batches (minimum of 3) should be based on the variability of the process, the complexity of the process / product and the experience of the manufacturer. For other specialised non-standard processes (described in section 8), data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of products by essentially equivalent processes." This section of the guideline is long, a bit confusing, and sometimes redundant, e.g. non-standard processes and the need for production scale data are also covered in in lines 237-244. Furthermore, some of the examples provided of 'non-standard methods' can become, over time, more common. Such definitions could change with time and experience. We recommend the following deletions of text in this paragraph. The stipulation of the number of batches needed in some cases is inconsistent with the ICH principles and unnecessary. **Proposed change (if any):** We propose the following edits in this section: "~~In certain cases however,~~ It ~~is~~ **may** be ~~considered~~ necessary to provide production scale validation data in the marketing authorisation dossier.~~ e.g. in those circumstances where the product is a biological / biotech product, where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale, or for specialised products such as certain modified release preparations (for medicinal products for human use, see the Note for guidance on quality of Modified release products; for those for veterinary use, see the Note for guidance on the Quality of Modified Release Dosage Forms for Veterinary Use).~~ Where non-standard sterilisation methods or aseptic processing are employed, data should be provided ~~on~~ **from** a number of ~~consecutive~~ batches at production scale prior to approval. The number of batches ~~(minimum of 3)~~ should be based on the samples and the data needed to address **the** variability of the process, the complexity of the process / product and the experience of the manufacturer. ~~For other specialised non-standard processes (described in section 8), data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of~~	

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			~~consistent manufacture of products by essentially equivalent processes."~~ With all shown changes made, the section would read: "It may be necessary to provide production scale validation data in the marketing authorisation dossier. Where non-standard sterilisation methods or aseptic processing are employed, data should be provided from a number of batches at production scale prior to approval. The number of batches should be based on the samples and the data needed to address the variability of the process, the complexity of the process / product and the experience of the manufacturer."	
9	Section 5.1. Traditional process validation Lines 130-132		**Comment:** This sentence is a repeat of the text in lines 109-111 above, it reads, "*A justification for the chosen process validation studies should be presented in Module 3 and the Quality Overall Summary for human medicines, and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines*." **Proposed change (if any):** Delete redundant text at 130-132, ~~"A justification for the chosen process validation studies should be presented in Module 3 and the Quality Overall Summary for human medicines, and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines."~~	
10	Section 5.1. Traditional process validation Lines 133-136		**Comment:** This section reads, *"If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. Validation at production scale may be conducted step-wise when the manufacturer moves to different areas of the design space."* It is unclear how this can be accomplished. The verification of design space presumably requires process parameters to be run outside of the normal operating ranges specified in the commercial batch records. Therefore, verification of design space established using qualified, scaled down models seems excessive at commercial scale.	

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			Conducting step-wise validation is confusing and inhibits design space development since more validation work may need to be interpreted than a traditional development approach. **Proposed change (if any):** Suggest deleting sentence (line 135-136) With suggested changes these sentences should read, "If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. ~~Validation at production scale may be conducted step-wise when the manufacturer moves to different areas of the design space.~~"	
11	Section 5.2. Continuous process verification Lines 138-139 Lines 165-169		**Comment:** The current statements read, "Continuous Process Verification (CPV) is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8)." "A discussion on the appropriateness and feasibility of the CPV strategy should be included in the development section of the dossier and should be supported with data from at least lab or pilot scale batches. A description of the CPV strategy including the process parameters and material attributes that will be monitored as well as the analytical methods that will be employed should be included as described in Annex 1, with cross reference in the validation section of the dossier." The use of the terms "Continuous Process Verification" and "Continued Process Verification" can be confusing, especially where the CPV acronym is used. Their similarity makes it difficult to understand that the first term suggests an alternative approach to traditional PV, whereas the second term is applicable to all products and needs to be performed throughout the lifecycle. **Proposed change (if any):** In order to avoid confusion, PDA recommends that the terms be written out whenever they are used, and the acronym "CPV" not be used in the guideline.	

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			These statements would then read, "Continuous ~~P~~ process ~~V~~ verification ~~(CPV)~~ is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8)." "A discussion on the appropriateness and feasibility of the ~~CPV~~ **continuous process verification** strategy should be included in the development section of the dossier and should be supported with data from at least lab or pilot scale batches. A description of the ~~CPV~~ **continuous process verification** strategy including the process parameters and material attributes that will be monitored as well as the analytical methods that will be employed should be included as described in Annex 1, with cross reference in the validation section of the dossier."	
12	Section 5.2. Continuous process verification Lines 144-146		**Comment:** The first sentence of this statement reads, *"Relevant process quality attributes of incoming materials or components, in-process material and finished products should be collected."* The term 'process quality attributes' is not an ICH or otherwise recognized definition in the industry. Deletion of the word 'process' will allow this sentence to read more clearly. **Proposed change (if any):** Change "process quality attributes" to "quality attributes," so the statement reads, "Relevant ~~process~~ quality attributes of incoming materials or components, in-process material and finished products should be collected."	
13	Section 5.2. Continuous process verification Line 169-171		**Comment:** The guideline reads, "*Actual data generated during continuous process verification at commercial scale should be held at the site for inspection*." From a GMP compliance perspective, regulators have long permitted archiving of data off-site and/or at centralised locations and not "held" at the site. The expectation is that the relevant data can be made available for inspection at the site of the inspection when requested.	

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			Proposed change (if any): Change the word 'held' to 'available' to read, "Actual data generated during continuous process verification at commercial scale should be ~~held~~ **available** at the site for inspection."	
14	5.2. Continuous process verification Lines 171-174		**Comment:** The sentences read, *"The applicant should define the stage at which the product is considered to be validated and the basis on which that decision was made. The discussion should include a justification for the number of batches used based on the complexity and expected variability of the process and existing manufacturing experience of the company."* **Proposed change (if any):** Consistent with the concept of PV over the product lifecycle, we suggest modifying the sentences to read: "The applicant should define the stage at which the product is considered to be ~~validated~~ **under control and available for commercial distribution,** and the basis on which that decision was made. The discussion should include a justification for the number of batches used based on the complexity and expected variability of the process and existing manufacturing experience of the company."	
15	Section 8. Standard vs. non-standard methods of manufacture Line 273-278		**Comment:** Current text bullets read, • "Processes with critical steps such as lyophilisation, microencapsulation; • Processes where the physicochemical properties of the active substance or a key excipient (e.g., lubricant, coating agent) may give rise to processing or scale up difficulties, or stability problems during manufacture at larger scale for related products; • Any request for real time release testing; • Aseptic processing." We recommend deletion of line 277, "Any request for real time release testing;" from the above bulleted list. Real time release should not be considered as a "specialized or complex"	

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			process requiring process validation data be included in the initial dossier submission. In addition, if this recommendation remains in the guideline, it would create a strong disincentive for adoption of this new technology. Real time release can provide a higher assurance of product quality, relative to the more traditional end product testing regimes. Real time release testing is combining measurements and process controls and unlike the other 3 bullets which are manufacturing processes. **Proposed change:** The revised bullets would read, • "Processes with critical steps such as lyophilisation, microencapsulation; • Processes where the physicochemical properties of the active substance or a key excipient (e.g., lubricant, coating agent) may give rise to processing or scale up difficulties, or stability problems during manufacture at larger scale for related products; • ~~Any request for real-time release testing~~ • Aseptic processing."	
16	Annex I: Process Validation Scheme Lines 353-354		**Comment:** This sentence states, "Following completion of the scheme, a report containing the following information and signed by the appropriate authorised person should be generated and made available for inspection:" We suggest further clarification regarding the identity and/or function of the 'appropriate authorised person' who signs the report. **Proposed change (if any)**: Revise the sentence to change 'appropriate authorised person to 'site Quality Assurance...', which will then read as follows: "Following completion of the scheme, a report containing the following information and signed by ~~the appropriate authorised person~~ **site Quality Assurance** should be generated	

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			and made available for inspection:"	
			END	