25 October 2012

Quality Working Party
European Medicines Agency
7 Westferry Circus
Canary Wharf
London E14 4HB
United Kingdom
Email: qwp@ema.europa.eu

Subject: Submission of comments for "Draft guideline on process validation"
Reference: EMA/CHMP/CVMP/QWP/70278/2012-Rev1

Dear Sir/Madam:

ISPE welcomes the opportunity to comment on the "Draft guideline on process validation". The comments provided reflect the both the very fruitful discussions that delegates enjoyed with QWP members at our September conference in Brussels and the views of members from a diverse range of pharmaceutical companies and providers.

As discussed in Brussels, our members would welcome the opportunity to continue to support the endeavors of the QWP through finalization and implementation of the guideline, and in the future development of Annex 15, which we hope will lead to further convergence and harmonization of the international expectations for validation.

Our comments are attached.

Yours sincerely,

President/CEO, ISPE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2012

Guideline on Process Validation (EMA/CHMP/CVMP/QWP/70278/2012-Rev1)

Comments from:

Name of organisation or individual
ISPE

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	It is suggested that the title of the document be adjusted to more closely reflect its purpose. It is suggested that the "Guideline on Process Validation" be changed to "Guideline on Process Validation Information to be Included in Regulatory Submission" or similar.	
	It would be desirable to have additional information about statistical expectations in PV (if any) included in Annex 15 when revised.	
	When Annex 15 is revised, it would be desirable to have terminology harmonized with ICH and FDA PV Guidance, where possible. Explanation of any intended differences would also be helpful.	
	It is suggested that the use of "continued" and "continuous" be clarified throughout the document: ISPE members are voicing concerns over mis-interpretation and recommend emphasising the differences. It may be helpful to create a separate section discussing implementation of advanced technologies for products already commercialized. It seems some of these are intermingled in other sections at present, which can be confusing. Using "advanced technology/PAT rather than "continuous verification" where appropriate may also improve clarity.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
41 (and 318)		Delete “and quality attributes” since by definition a specification includes the quality attributes (Q6A and Q6B).	
60		Scope – We suggest modifying the scope to more clearly reflect the purpose of the document, ie., The intent of this document is to provide expectations for validation related information to be included in the registration dossier. This document should be utilized in conjunction with Annex 15, which explains compliance expectations associated with conducting PV.	
60		Scope – Since 2003/63/EC directs that process validation studies shall be provided for active ingredients ‘as appropriate’, it is suggested that the scope reference ICH Q11 as containing the registration expectations for active ingredients and, therefore, this information is not repeated in this guide.	
112 -113		A control strategy contains elements more than critical process parameters (definition ICH Q10) and therefore suggest “which primarily includes critical process parameters” is redundant and should be deleted	
128		It is recommended that this sentence be either deleted or changed to be more easily understood and consistent with 2003/63 and ICH guidelines. It is not clear what ‘those phases’ are. Since contemporary use of the word ‘phase’ is usually in reference to a part of the lifecycle (Line 311), at least this word should be replaced by ‘stages’ or ‘steps’. Is the	

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		intent to refer to 'phases (steps)' not controlled with the specification? A specification does not usually control a step, only provide assurance of the product quality (Q6A/B). We propose; "Where it is necessary to provide production scale validation data in the dossier, the validation studies should address those manufacturing steps deemed to be critical." It is not necessary to suggest 'by additional testing as necessary' since this implies that additional testing might not be required and then the only outcome is that the test data are captured in both the batch record and in a validation report.	
133		Suggest change from "if a design space is implemented" to "if a design space is to be proposed in the dossier". This is more consistent with purpose of the document – validation related information to be included in submission. Additionally, suggest a change from "should provide the validation strategy at production scale" to "should provide verification strategy to show the model is representative of full scale." We consider models to be subject to verification not validation. The guide does not indicate validation expectations when a proposed design space does not use a model (in the chemometric sense) or where a design space is based on dimensionless attributes. We suggest " Similarly, where a design space is proposed that does not use a statistical model, the applicant should provide a verification strategy to show that the design space is representative of full scale."	
135		"Validation at production scale may be conducted step-wise..." We recommend to delete or revise this sentence. The extent of validation activity, if any, associated with movement within a design space should be commensurate with the science, risk	

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		and any control strategy modifications. Additionally, most design space movements would likely occur post-approval, which this guideline does not address.	
156 and 160		Delete “and commercial experience”, since this guideline is discussing the information to be submitted in the application prior to commercial sale.	
162 and 170		Change “commercial” to “production” to be consistent with the rest of the guideline.	
163		Change to ‘If a design space if proposed…..’	
172 -3		Change ‘was’ to ‘will be’ and ‘used’ to ‘to be used’ since the decision occurs in the future.	
179		Delete the whole paragraph. It is not clear how one measures CPV performance. Additionally, the totality of product quality depends on compliance with GMP principles, not just CPV, and so this section is redundant.	
184		Reword this sentence to be consistent with the scope of the guideline applying to the information to be submitted in the application. E.g., “The applicant may choose to use either…. It should be clear which approach to validation will be taken….the number of batches will depend upon…..”	
189		Delete the sentence. We believe that CPV can provide an equivalent, or even higher, assurance of quality for both standard and non-standard processes and thus all three options should be available to the applicant. Section 8 line 229 does suggest the acceptability of CPV for non-standard processes. If this recommendation is accepted, the sentence at line 255 can also be deleted.	
191		We suggest that 5.4 be made into a stand-alone section (eg,	

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		Section 6) to help reduce ambiguity. As a subsection of 5, it could appear that continued process verification is an option in the same way as the hybrid approach or continuous verification. In fact we believe that continued process verification is not optional and the guide should make it clear that it is an expectation irrespective of the approach used.	
201		Continued process verification should entail enhanced sampling and monitoring, dependent upon process variability, otherwise there is no difference from the normal (registered) control strategy. We recommend that the sentence be amended to “Hence, according to the performance and variability of the process, defined periods of enhanced sampling and monitoring should be established to provide increased process understanding as part of continual improvement.”	
203		Change “continuous” to “continual” (Q10).	
203		Insert a comma “If high impact models are used, as part” since the models are not themselves used as part of the process verification.	
237-239		The Guide states, “The following categories are examples of products or processes which could be considered as non-standard, and for which production scale validation data might need to be provided in the marketing authorisation application dossier, unless otherwise justified:...” Suggest adding another sentence suggesting some basis by which applicants could justify that a process is standard for them, such as, “An applicant could potentially justify that a process is standard, based on experience with similar processes, products, number	

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		of batches manufactured with a similar process, similar process capability analysis, excipient and control strategy risk assessments, etc."	
339		No information is given on criteria to determine the number of PV batches except it would "usually be a minimum of 3" batches. It is unclear whether a "default" of 3 is acceptable or whether further rationale is required. If statistical criteria are intended, it should so state.	

Please add more rows if needed.