29 October 2014

European Medicines Agency
Committee for Medicinal Products for Human Use (CHMP)
7 Westferry Circus
Canary Wharf
London E14 4HB United Kingdom

Subject: EMA/CHMP/BWP/187338/2014
Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

Dear Sir or Madam,

Thank you for the opportunity to comment on the above draft guideline. The draft was reviewed by members of the ISPE process validation technical community. We are pleased to offer specific comments to the draft as detailed in the attachment to this letter.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Yours sincerely,

John Bournas
President/CEO, ISPE

28 Oct 2014

Submission of comments on 'Guideline on Process Validation for the Manufacture of Biotechnology-derived Active Substances and Data to be provided in the Regulatory Submission '

(EMA/CHMP/BWP/187338/2014

Comments from:

Name of organisation or individual
International Society for Pharmaceutical Engineering (ISPE) 600 N. Westshore Blvd., Suite 900 Tampa, Florida 33609 USA +1 813-960-2105 regulatorycomments@ispe.org

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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

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)*
35		Comment: Enhance development and enhanced validation are used very closely and could cause confusion. Particularly as enhanced validation may not have any relationship with enhanced development and enhanced validation is not referred later in the text. Proposed change: Recommend using alternate approaches for validation (as used in line 163) when referring to non-traditional validation approaches.	
35		Comment: Need to clarify "enhanced validation**"**. This could be done in the "Definitions" section or a new section (see below). Proposed change: Add definition of "enhanced validation". It is not very clear whether "enhanced validation" approaches includes traditional x runs or x runs prospective and Continuous Process Verification or prospective x runs and future x On-going Process verification? More explicit examples in a new section (rather than in the "Definitions" section and embedded in multiple sections) would be an alternative that would help greatly.	
124-128		Comment: The examples used in this section (particularly "cumulative hold studies") give concern. The event of a	

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		cumulative hold would be extremely unlikely. At scale simulation of a cumulative hold is inconsistent with current validation study design and may be impractical for many long biological processes. As scientifically justified physiochemical hold time studies at a representative small scale may provide the required robust data. Similarly abnormal or spiking studies cannot be done at scale due to risk to product and are much better done in representative small-scale studies. Proposed change Text needs to clarify that some of the work could be done as representative small scale. Abnormal conditions would definitely not simulate at scale. Suggest using alternate examples.	
211 - 217		Comment: We suggest to link this section to ICH Q 11 For validation full-scale equipment has to be used. Guidance as written appears to preclude any small scale data which can be scientifically justified to provide relevant process development data. Similar to qualifying small scale chromatographic resin characterization, lot-to-lot variability should be well represented by small scale studies with various lots. Proposed change: While small scale data are relevant for process development, process verification for disposable systems should be done with full scale equipment. Small-scale data with various batches of disposables should be provided and where feasible process verification should also use various batches for	

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		process verification studies. .	
295		Comment: Shipping and transport validation. Annex 15 EU GMP describes shipping and transportation verification rather than validation. Proposed change Verification seems more appropriate since transportation has a high degree of variability and cannot really be validated in the true sense.	
317		Comment: Suggest incorporating a definition for "small scale" Proposed change Small scale batches are any scale smaller than full scale commercial batch size e.g. pilot scale, or lab scale	
359		Comment: ICH 11 refers to ICH 8 Proposed change Suggest incorporating ICH Q 8 in the reference list	

Please add more rows if needed.