Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

October 28, 2014

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: 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 2
Committee for Medicinal Products for Human Use (CHMP)

Dear Sir/Madam,

PDA is pleased to see the continuing updating of process validation related guidelines and legislation across Europe. Our comments are primarily intended to further strengthen the alignment and harmonization among these documents and with other global guidelines.

PDA recommends terminology and definitions throughout this guideline be harmonized with other regulatory authorities and include the concepts of lifecycle approach to process validation as per ICH Q8, Q9 and Q10. The use of common language can improve understanding across cultural boundaries and streamline the submission process for both applicants and reviewers.

For example the use of the term "process evaluation" may create confusion since process evaluation is typically performed for process changes and on-going monitoring. Perhaps calling it "process characterization and validation studies" may be helpful because it aligns with Annex 15 and would differentiate from full-scale process verification. Also consider Process "Validation" instead of "Verification" for consistency with draft Annex 15 terminology.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing and process validation representing our Board of Directors, our Science Advisory Board, our Biotechnology Advisory Board and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Georg Roessling, Ph.D.
Senior Vice President, PDA Europe
Roessling@pda.org

Cc: Richard Johson, PDA, Denyse Baker, PDA
Attachment

<31 Oct 2014>

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 2
Committee for Medicinal Products for Human Use (CHMP)

Comments from:

Name of organisation or individual
PDA (The Parenteral Drug Association)

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).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	PDA recommends terminology and definitions throughout this guideline be harmonized with other regulatory authorities and include the concepts of lifecycle approach to process validation as per ICH Q8, Q9 and Q10. The use of common language can improve understanding across cultural boundaries and streamline the submission process for both applicants and reviewers. For example the use of the term "process evaluation" may create confusion since process evaluation is typically performed for process changes and on-going monitoring. Perhaps calling it "process characterization and validation studies" may be helpful because it aligns with Annex 15 and would differentiate from full-scale process verification. It is understood that process characterization and validation studies are performed prior to process verification. See also comments to lines 50-57.	

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)*
32		**Comment:** The opening sentence states that the guideline covers"biotechnology derived proteins" but later in the scope section (lines 65 and 66), it states that polypeptides are covered by the guidance. **Proposed change (if any):** The guideline covers process validation of biotechnology-derived proteins **and polypeptides**…	
36-37		**Comment**: The statement referencing "enhanced approach to process validation" is unclear or perhaps in error. Is this intended to refer to an "enhanced approach to development?" PDA is not aware of a definition for "enhanced approach to validation" and doesn't see another section referring to this concept. **Proposed change (if any):** PDA recommends clarification of this statement.	
41-43		**Comment:** Align guideline with the wording used on the EMA guideline on PV for finished products (EMA/CHMP/CVMP /QWP/BWP/ 70278/2012-Rev 1- Feb 2014). **Proposed change (if any):** Add the following text per EMA PV guide: **"Process validation should not be viewed as a one-time event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production."**	
50-57 and		**Comment: The Terms** "*Process Evaluation*" and "*Process Verification*" are interpreted differently by different health authorities and different guidances and so don't clearly	

<table>
<tr><th>Line number(s) of the relevant text

(e.g. Lines 20-23)</th><th>Stakeholder number

(To be completed by the Agency)</th><th>Comment and rationale; proposed changes

(If changes to the wording are suggested, they should be highlighted using 'track changes')</th><th>Outcome

(To be completed by the Agency)</th></tr>
<tr><td>102-104; 216</td><td></td><td>differentiate in which CTD section the information should be submitted S.2.5 or S.2.6.

Proposed Change: To avoid confusion in the industry, PDA recommends EMA harmonize terminology with other regulatory bodies. In addition, PDA recommends that EMA consider Process “Characterization” instead of or in addition to “Evaluation”. Characterization encompasses many types of studies (e.g. designed experiments and robustness studies as described in ICH Q8).

And consider Process “Validation” instead of “Verification” for consistency with draft Annex 15 terminology. (Please note that section 6.2.3 of this draft uses “validation” terminology in reference with reprocessing.) Other lines in this draft where PDA recommends changing the term “verification” include 102-104 and 216.

As a tool to help clarify its recommendations, PDA submits the following table for placement of the different types of information into the corresponding CTD sections.

<table>
<tr><th>Submission Content</th><th>Recommended CTD Section Number</th></tr>
<tr><td></td><td></td></tr>
<tr><td>On-going process verification (after Approval)</td><td>S.2.5 or S.2.4</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Process evaluation + Process qualification = Process validation</td><td>S.2.5</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Process development</td><td>S.2.6</td></tr>
</table>
</td><td></td></tr>
<tr><td>77</td><td></td><td>Comment: When describing process development the draft states “Although not</td><td></td></tr>
</table>

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)*
		considered as part of process validation..." In PDA's experience, process design is the beginning of the process validation lifecycle, so this statement does not support a lifecycle approach. The statement that "process validation does not end at the time of marketing authorization" (line 46) does support the lifecycle. **Proposed change (if any):** Delete the phrase ~~Although not considered as part of process validation~~..and begin sentence "**Process development is an essential foundation for process validation.**"	
110-111		**Comment:** PDA suggests that "control strategy" be used instead of "control" since a comprehensive control strategy includes BOTH control and monitoring and the word "control" suggests inputs only. Control Strategy is also terminology consistent with ICH. **Proposed change (if any):** Successful process evaluation should thus demonstrate that the design of the manufacturing process and its control **strategy** are appropriate for commercial manufacturing.	
Sections 6.1 – 6.22		**Comment:** Sections 6.1 to 6.2.2 are very specific to the upstream and downstream portions of a typical cell culture process. The scope of the document is wider than cell culture and protein production. These sections would be more valuable if they were a statement of principles for PV rather than a worked example of how a cell culture process should be validated. **Proposed change (if any):** It should be acknowledged in section 6.1 that not all recombinant protein products under the scope of this guidance will include a only a cell culture step in the upstream process, therefore additional unit operations in the upstream process should be addressed in this section.	
121		**Comment:** There is no definition of proven acceptable range (PAR) or reference to the definition. Some may not be familiar with the term.	

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)*
		Proposed change (if any): PDA recommends adding the ICH Q8(R2) definition of PAR to the glossary.	
124		**Comment:** PDA recommends that the identification of "worst case" should cover any process variations that can be foreseen. The use of the term "abnormal conditions" suggests it is necessary to test unexpected and unforeseen conditions. PDA recommends that this guideline avoid suggesting that a process be run under abnormal or uncontrolled conditions. In general procedures are in place to determine what should be done with unexpected conditions. **Proposed Change:** … Delete "abnormal conditions"	
124		**Comment:** Cumulative hold time is not appropriate worst case for biologics. Some readers may take this list of examples to exclude other characteristics, so a list of examples may not be valuable. **Proposed Change:** *PDA recommends to delete the examples because worst case should be determined on a case by case basis for each process.*	
215-216		**Comment:** It is unclear in the current text whether **"**Various batches of disposable systems…" is intended to mean various batches of flexible disposable materials making up a disposable system or various batches of biotech active ingredient or intermediate. **Proposed change (if any):** PDA recommends changing as follows: Various batches of disposable **components** should be used..."	
265-8		**Comment:** Current industry practice is full scale verification is performed near the end-	

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)*
		of-life of the column, which was estimated and established at small scale. **Proposed change (if any):** Considering the number of purification cycles required for this evaluation, small scale studies are considered appropriate to **initially** estimate ~~and set~~ the maximum, number of cycles at the time of regulatory submission**(except for viral clearance purification cycles)**., provided that full scale verification is performed on an ongoing basis to confirm the column performance and integrity, in accordance with an approved protocol. **For viral clearance purification steps the maximum number of cycles must be determined in small scale at the time of regulatory submission and for additional extensions in maximum numbers of cycles determined in small scale in accordance with an approved protocol.**	
285-286		**Comment:** Full scale study is required for microbial hold, but worst-case small scale studies would be sufficient to establish chemical stability. The word 'Additionally' may be interpreted as both full-scale and small scale studies are required. **Proposed change (if any): However, lab-scale studies could ~~additionally~~** be considered if appropriately justified.	
303-304		**Comment:** Comparable outputs may not always be achieved using the same input ranges due to differences in manufacturing technologies requiring various control strategies. **Proposed Change:** "The adapted process should be capable of achieving comparable outputs. ~~when operating within the same input ranges~~"	

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)*
306		**Comment:** Considering lifecycle approach of process validation, it is not clear what documentation would be required to satisfy "it must be demonstrated that the subsequent site has reached a validated state." **Proposed change (if any): "...**it must be demonstrated that ~~that the subsequent site has reached a~~ **the process is** validated ~~state~~ **at a subsequent site**.	
336-339		**Comment:** In PDA's experience, NORs are submitted as part of the verification studies, as noted in section 5.2. PDA recommends deleting reference to submission requirements in this definitions section. PDA would also like to suggest a more specific definition as taken from Technical Report 60 " **Proposed change (if any):** Replace the current definition with the following **A defined range, within or equal to the Proven Acceptable Range specified in the manufacturing instructions as the target and range at which a process parameter is controlled while producing unit operation material or final product meeting release criteria and Critical Quality Attributes**	

Please add more rows if needed.