EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2014

Submission of comments on Revision of Annex 15: Qualification and Validation

Comments from:

Name of organisation or individual
E.I.P.G. ..... www.eipg.eu

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)*
	1. This Guidance is a true evolution which effectively integrates both risk analysis and mechanistic approaches to quality, in connection with QbD. 2. A few new terms and definitions are present in the Glossary. There is the need of an alignment of the terms with new EMA guideline on Process Validation and with the Glossary of Volume 4 – EU GMP 3. Retrospective validation is no longer described as this seems not to be in line with the new approach to validation. However, for legacy products retrospective validation would be still in use. 4. As for process validation (Chapter 4) an exception should be made for IMP's, where process can't be fully validated (compare 9.12 for cleaning validation). 5. It would be helpful to dedicate a chapter to quality risk management tools that can be used in qualification/validation approaches to assess critical quality attributes and critical process parameters.	

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)*
Principle			
Principle		**Comment:** Reference to ICH Q 9 is missing. **Proposed change (if any):** *The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.*	
1.3		**Comment:** The oversight of the quality function on validation activities should be clearly required, in alignment with EU GMP Chapter 1 and 2. **Proposed change (if any):** *Even though validation personnel may not report necessarily to a quality function of the organization, appropriate oversight by a quality function over the whole validation life cycle should be maintained.*	
1.5		**Comment:** As qualification is used further in the annex, qualification should be added to increase transparency. **Proposed change (if any):** *a) Validation and qualification policy*	

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1.5		**Comment:** A document of high profile like a VMP should not contain any "*confirmation*" about materials used for validation, as "*confirmations*" are more typical of a reporting type document and not of a direction type document. **Proposed change (if any):** Delete 1.5 k).	
1.5		**Comment:** Out of specifications are not mentioned. **Proposed change (if any):** *g) Handling of acceptance criteria and OOS*	
2.2 and 2.9 and 11.5		**Comment:** The terms "*appropriate personnel*" and "*relevant responsible personnel*" are reported. These qualities should be defined more functionally, in line with EU GMP Chapter 2. **Proposed change (if any):**	
2.4		**Comment:** Test methods do also determine criteria for attributes and parameters **Proposed change (if any):** *…attributes and parameters which are important, test methods and the acceptance criteria for each.*	
2.6		**Comment:** The term "deviation" should be added to the Glossary.	

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		Depending on the change, the deviation process can be appropriate, but minor changes shouldn't be handled through the deviation process. Appropriate documentation remains important for any changes, including review by QA. **Proposed change (if any):** *Any change to the approved protocol during execution should be documented, assessed and, if considered relevant, documented as a deviation, scientifically justified*.	
2.7		**Comment:** Not meeting pre-defined acceptance criteria can be documented in a deviation, an OOS or in the validation documentation as such. **Proposed change (if any):** *Results which fail to meet the pre-defined acceptance criteria should be evaluated and, if appropriate, recorded as a deviation, be fully investigated and any implications for the validation discussed in the report.*	
3		**Comment:** An overall protocol describing all stages of qualification is not specified. This could be a very useful umbrella document to improve transparency and clarity on the qualification approach. **Proposed change (if any):**	
3		**Comment:**	

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		In some cases there are still legacy equipment/utilities operational. This should be addressed by considering a retrospective validation approach, where possible . **Proposed change (if any):**	
3.3		**Comment:** DQ should be limited to more complex projects, like new facilities and systems, excluding equipment. **Proposed change (if any):** "*The next element in the validation of new facilities or systems could be DQ… "*	
3.7		**Comment:** The tests executed during SAT are often repeated during IQ and OQ. It would be useful to describe how SAT testing can be leveraged into IQ/OQ documentation e.g. upfront agreed upon and QA approved. **Proposed change (if any):**	
3.8		**Comment:** Clarification would be required about "repaired or rebuilt or renovated" equipment. In these cases, subject to a justified risk assessment, URS and FAT/SAT stages may not be required, particularly if the work is carried out at the site of installation. Alternatively, a definition of "modified equipment" that includes repaired, rebuilt or renovated equipment should	

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		be added to the Glossary, with the additional statement about URS and FAT/SAT stages. **Proposed change (if any):**	
3.11		**Comment:** Calibration should be included as a specific item to be considered, next to maintenance plan finalization. **Proposed change (if any):**	
3.9, 3.10, 3.14		**Comment:** Typing error **Proposed change (if any):** *IQ (OQ, PQ) could include, but is not limited to the following*	
3.12		**Comment:** Maintenance schedule should be included as part of the PQ completion. **Proposed change (if any):**	
4.		**Comment:** Revalidation is not mentioned in this chapter 4. This should be added as it is relevant, also to be consistent with point 1.5 j) where revalidation is mentioned **Proposed change (if any):** Addition, after point 4.29, a chapter as follows: ***Revalidation*** *In certain cases, revalidation is applicable, e.g recurrent*	

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		media fill in sterile manufacturing	
4.3		**Comment:** This section is more related to the process than to the product **Proposed change (if any):** "*Manufacturing processes may be developed using …"* **Comment:** It is to be clarified how a continuous verification approach would require a prospective validation approach to be followed. **Proposed change (if any):**	
4.4		**Comment:** The bracketing approach is a science and risk based approach. This should be reflected as such. **Proposed change (if any):** *" … the number of validation batches could be reduced by the use of a science and risk based approach (e.g. bracketing)"*	
4.8		**Comment:** Clarification should be given about the qualification of legacy utilities and systems (e.g. WFI installation). A provision to cover those systems should be incorporated in the annex. **Proposed change (if any):**	
4.12		**Comment:** Proposal to replace "state of control" to "process control	

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		strategy". **Proposed change (if any):** *It is especially important that the underlying process knowledge for the design space justification (if used), and for development of any mathematical models used to establish a process control strategy.*	
4.19		**Comment:** Critical material attributes should also be included, as it is specified at Point 4.22. In fact, it is to make clear that CQAs include also incoming starting materials (bulk active and excipients). The definition of CQA in the Glossary should be amended accordingly. **Proposed change (if any):**	
4.20		**Comment:** The list of inclusions in validation protocols should also contain the quali-quantitative formula (product specifications) and the anticipated batch/lot sizes. **Proposed change (if any):**	
4.20		**Comment:** Section e and f should be merged into one section (typing error). **Proposed change (if any):**	
4.23		**Comment:** The reference is not correct. It should be 4.1-4.13.	

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		Proposed change (if any):	
5		**Comment:** Any transport validation or verification should be covered in GDP guidance (2013/C343/01), which already covers qualification/ validation / verification for certain subchapters (Equipment) as well as in the Glossary (definitions). Chapter 5 could be deleted and the contents moved to next GDP revision draft for further discussion. **Proposed change (if any):** Delete Chapter 5.	
6		**Comment:** As primary packaging is considered as an integral part of the medicinal product, this aspect should be captured in the section on process validation in chapter 4. **Proposed change (if any):** Delete chapter 6, or move them as a subchapter under chapter 4. Process validation	
6.1		**Comment:** Typing error **Proposed change (if any):** *" …significant impact on the integrity …"*	
7		**Comment:** The contents of this chapter is actually covering qualification of utilities, and should therefore be incorporated under chapter 3. Qualification stages for (…) utilities. **Proposed change (if any):**	

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		Move chapter 7 as a subchapter under chapter 3.	
8.1		**Comment:** GMP chapter 6 does not describe how to validate analytical methods. Reference to corresponding ICH guidelines for validation of analytical methods should be made **Proposed change (if any):**	
9.4		**Comment:** As the equipment is also part of the system undergoing a cleaning process, it would be better to specify it. **Proposed change (if any):** "*Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated"*	
9.5		**Comment:** These requirements are to be aligned with the guidance on setting health based exposure limits, which is, at the moment, in a draft form. It seems reasonable to say that these requirements are strictly linked to the approval of the guidance currently under discussion. Reference should also be made to the revised EU GMP Chapters 3 and 5. **Proposed change (if any):** "*Limits for the carry-over of product residues should be set up*	

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		according to the applicable guidance"	
9.8		**Comment:** In a worst case approach, an alternative product may be selected for cleaning validation purposes, simulating the toxic / hazardous product. **Proposed change (if any):**	
11.6		**Comment:** The sentence is not clear. It is to be clarified or deleted **Proposed change (if any):**	
GLOSSARY **Change Control**		**Comment:** Change Control is important to assure and maintain also the compliance with the Marketing and Manufacturing Authorization. **Proposed change (if any):** *"….that might affect the validated status and the compliance to the Marketing and Manufacturing Authorizations of facilities, systems, equipment and processes, as applicable. The intent is to determine the need for action to ensure and document that the system is maintained in a validated status and compliant with the relevant Marketing and Manufacturing Authorizations"*	
GLOSSARY **Cleaning Validation**		**Comment:** The residues of cleaning agents and microbial contaminations of surfaces in contact with the product have also to be	

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		considered in cleaning validation. **Proposed change (if any):** *"…will remove all traces of the previous product used in the equipment, of the cleaning agents used in the cleaning procedure and to assess the microbiological quality of the surfaces in contact with the product"*	
GLOSSARY **Cleaning Validation**		**Comment:** Cleaning verification is mentioned at Point 9.12, but it is not defined. Cleaning verification definition should be added. **Proposed change (if any):**	

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Please add more rows if needed.