EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2014

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

Comments from:

Name of organisation or individual
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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)*
	1. For IMP's in the early phases (I and II) the processes and analytical methods are not fully validated. This should be clarified in the principle. 2. Retrospective validation is no longer described. For legacy products this would be useful. 3. The Glossary should be incorporated and aligned with the general Glossary document for Volume 4. For example confusion can be caused among 'Process Validation' in current draft vs. 'Validation' in general glossary, which also covers validation of process among others. In the General Vol 4 glossary, it is mentioned under Qualification that 'The word Validation is sometimes widened to incorporate the concept of qualification', which is a useful clarification. 4. Utilities and systems are used interchangeably. We recommend to use the same terminology be used throughout the text wherever possible. 5. It would be helpful to dedicate a chapter to quality risk management tools that can/should 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:** 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:** Validation personnel (as other personnel) should be part/integrated in the overall quality system of the company. The QA department will/can oversee the validation activity directly or indirectly (by means of audit). Align with GMP chapter 1 and 2. **Proposed change (if any):**<br~~Validation personnel~~Personnel conducting validation should report as defined in the pharmaceutical quality system ~~although this may not necessarily be to a quality management or a quality assurance function, however there should be~~ in order to assure the appropriate quality oversight over the whole validation lifecycle.	
1.5		**Comment:** As qualification is used further in the annex, qualification should be added to increase transparency. **Proposed change (if any):**	

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		a) Validation and qualification policy	
1.5		**Comment:** As the VMP is a summary document data also can be referenced instead of contained in the VMP. **Proposed change (if any):** The VMP should be a summary document which is brief, concise, clear and contain or reference data on at least the following:	
1.5		**Comment:** The VMP is generally reviewed on a yearly basis; therefore there will be a gap between the current validation status and VMP. The review cycle of the VMP should be described in a company procedure. **Proposed change (if any):** c) Summary and scope of the facilities, systems, equipment, processes on site and the ~~current~~ validation status.	
1.5		**Comment:** Revalidation is not mentioned. This should be added as it will be relevant. E.g. recurrent media fill in sterile manufacturing. **Proposed change (if any):**	
1.5		**Comment:** Out of specifications are not mentioned. **Proposed change (if any):** g) Handling of acceptance criteria and Out Of	

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		Specifications (OOS)	
1.5		**Comment:** Point i is redundant as this is already captured in GMP Chapter 2. **Proposed change (if any):** point i) is to be omitted	
1.5		**Comment:** Point j could be rephrased. **Proposed change (if any):** j) ~~The ongoing validation strategy, including revalidation~~contain revalidation and / requalification, where applicable.	
1.5		**Comment:** In point k the appropriate level of qualification of suppliers is mentioned. However this his is already handled in the new GMP chapter 7. **Proposed change (if any):** k) Confirmation that the materials used for validation are of the required quality ~~and suppliers are qualified to the appropriate level.~~	
1.5		**Comment:** The VMP is too soon for statement k, move to IQ **Proposed change (if any):**	
1.6		**Comment:**	

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		A VMP is considered as an umbrella document, therefore this paragraph could be reworded in the light of complex projects. **Proposed change (if any):** For large and complex projects, planning takes on added importance and it may be necessary to create ~~a separate VMP~~separate project related documentation containing qualification strategy and planning.	
1.7		**Comment:** It is not clear what is meant by "risk assessment repeated". Can it be clarified what is meant by "repeated" or delete it? **Proposed change (if any):**	
2		**Comment:** It should be clarified what is in scope of the VMP. In the current version as well validation as qualification is in scope. **Proposed change (if any):**	
2.2 and 2.9 and 11.5		**Comment:** It is not clear what is meant by "appropriate personnel" and "relevant responsible personnel". Please align with GMP chapter 2. **Proposed change (if any):**	
2.2		**Comment:**	

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		The appropriate quality oversight is deemed necessary in the validation/qualification activities. **Proposed change (if any):** All documents generated during validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system with the quality oversight as appropriate.	
2.4		**Comment:** Test methods do also determine criteria for attributes and parameters **Proposed change (if any):** …attributes and parameters which are important **and test methods** and the acceptance criteria for each.	
2.6		**Comment:** Using the deviation system for any change is stricter in comparison with the current version of the annex. Depending on the changes 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. Deviation should be added to the glossary. **Proposed change (if any):** ~~Any~~ Relevant changes to the approved protocol during execution should be documented assessed and if necessary documented as a deviation and be scientifically justified.	
2.7		**Comment:**	

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		Not meeting pre-defined acceptance criteria can be documented in a deviation, an OOS or in the validation documentation as such, depending on the design and implementation of the GMP rules in the companies quality system **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.	
2.9		**Comment:** To better reflect current industry practice where stages can be combined e.g. IQ and OQ the paragraph needs to reworded **Proposed change (if any):** A formal release ~~for the next step in the validation process~~ prior to process validation should be authorised by the relevant responsible personnel either as part of the validation report approval…….	
3		**Comment:** Some equipment is COTS (e.g. analytical instrument) is delivered with a validation package of the supplier. For this type of equipment not all stages are as relevant as for customised manufacturing equipment. **Proposed change (if any):** Add an introduction before point 3.1. For some 'Commercial-of-the Shelf' (COTS) equipment	

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		delivered with a qualification package of the supplier, not all qualification steps as described below may be required.	
3		**Comment:** Are computerised systems in scope? This should be clarified and reference to annex 11 should be made. **Proposed change (if any):**	
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:** In some cases there are still legacy equipment/utilities operational. This should be addressed in chapter 3 of this annex. **Proposed change (if any):**	
3		**Comment:** Retirement of equipment is not mentioned in the life cycle approach. Could this be added?	

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		Proposed change (if any):	
3.3		**Comment:** DQ has no added value for small projects **Proposed change (if any):** 3.3. The next element in the validation of new facilities, systems or equipment **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):**	
3.8-3.14		**Comment:** The basis for IQ, OQ and subsequent qualification should be a criticality assessment based on risk assessment and regulatory compliance with a focus on patient safety and data integrity. This aspect could be further elaborated in the text. **Proposed change (if any):**	
3.9, 3.10, 3.14		**Comment:** Typing error **Proposed change (if any):**	

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		IQ could include, but is not ~~be~~ limited to the following	
3.11		**Comment:** The difference between "maintenance plans" and "preventative maintenance plans" is not clear. Maintenance is a preventative measure as such. **Proposed change (if any):** The completion of a successful OQ should allow the finalisation of ~~maintenance plans,~~ standard operating and cleaning procedures, operator training and preventative maintenance requirements.	
3.11		**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, e.g. recurrent media fill in sterile manufacturing; 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 media fill in sterile manufacturing	

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4.3		**Comment:** The first and the last sentence of this paragraph contain contradictory information. It is not clear whether a continuous verification or a prospective validation approach needs to be followed. Please clarify. **Proposed change (if any):**	
4.3, 4.24		**Comment:** The wording 'continuous' should be changed to 'continued' for clarity. **Proposed change (if any):** Medicinal products may be developed using a traditional approach or a ~~continuous~~ continued verification approach however irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market.	
4.4		**Comment:** The bracketing approach is a science and risk based approach. This should be reflected as such. **Proposed change (if any):** Process validation for new products should cover all intended marketed strengths and sites of manufacture, however for products which are transferred from one site to another or within the same site, and where there is existing product	

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		knowledge, including the content of the previous validation, the number of validation batches could be reduced by the use of a science and risk based ~~bracketing~~ approach (e.g. bracketing).	
4.4		**Comment:** The science and risk based approach should also be applicable for new products. **Proposed change (if any):**	
4.7		**Comment:** Batch size for proces validation should be scientifically justified or accepted. **Proposed change (if any):** 4.7. Normally batches manufactured for process validation **should justify the intended size** of commercial scale batches.	
4.8		**Comment:** Some utilities can be legacy systems e.g. WFI installation. A provision to cover those systems should be incorporated in the annex. **Proposed change (if any):**	
4.11		**Comment:** Proposal to include, besides the suppliers, also the materials	

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		as such to be qualified, and adding audits as appropriate. **Proposed change (if any):** Critical materials and ~~T~~the suppliers of critical starting and packaging materials should be qualified or audited as appropriate prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.	
		Comment: Proposal to replace 'state of control' to 'process control 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 ~~confirm a state of control should be available.~~establish a process control strategy.	
4.13		**Comment:** Proposal to clarify the paragraph. **Proposed change (if any):** Where validation batches are planned to be certified and released to the market this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the Marketing Authorisation or Clinical Trial Application.	

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4.14		**Comment:** It should be clarified what is meant by "authorised personnel" Align with GMP chapter 2. **Proposed change (if any):**	
4.20		**Comment:** 'process' is to be added before Validation protocols. **Proposed change (if any):** Process ~~V~~validation protocols should include, but are not be limited to the following:	
4.20		**Comment:** Section e and f should be merged into one section (typing error). **Proposed change (if any):**	
4.20		**Comment:** Product specifications are not mentioned. **Proposed change (if any):** Add following section before 'g)', and renumbering the following sections: g) Product specifications	
4.20		**Comment:** In section i acceptance criteria are mentioned. Testing should be performed with validated methods. It should even so be	

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		clarified that there can be testing be performed without predefined acceptance criteria and without validated methods e.g. characterization testing to enhance the process understanding. Depending on the stage of development The validation of analytical methods depends on the stage of development. For early phases (I and II) analytical methods are not fully validated. **Proposed change (if any):** i) Additional testing to be carried out, with acceptance criteria and validated analytical methods.	
4.23		**Comment:** The reference is not correct. It should be 4.1-4.13. **Proposed change (if any):**	
5		**Comment:** GDP guidance (2013/C343/01) covers transportation. Any transport validation or verification should be covered in GDP guidance, which already covers qualification/ validation / verification for certain subchapters (Equipment) as well as in the Glossary (definitions). Chapter 5 should be deleted and the contents moved to next GDP revision draft for further discussion. **Proposed change (if any):** Remove chapter 5 from Annex 15.	

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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	
7		**Comment:** The contents of this chapter named 'validation of utilities' is actually covering qualification of utilities, and should therefore be incorporated under chapter 3 Qualification stages for (…) utilities. **Proposed change (if any):** Move chapter 7 as a subchapter under chapter 3.	
8.1		**Comment:** GMP chapter 6 does not describe how to validate analytical methods. **Proposed change (if any):**	
8.1		**Comment:** Depending on the stage of development The validation of analytical methods depends on the stage of development. For early phases (I and II) analytical methods are not fully validated.	

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		Proposed change (if any):	
8.3		**Comment:** Proposal to change 'agents' into 'process' for clarity. **Proposed change (if any):** Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising ~~agents~~ processes do not influence the result.	
9.2		**Comment:** Requirement does not take into account dedicated equipment. **Proposed change (if any):** 9.2. A visual check for cleanliness may form an important part of the acceptance criteria for cleaning validation. **For non-dedicated equipment** however, it is not acceptable for this criterion alone to be used.	
9.4		**Comment:** Is this paragraph also applicable for equipment? If not please clarify. If yes see proposed change. **Proposed change (if any):** Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.	

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9.5		**Comment:** It is not explicitly mentioned validated methods are needed for cleaning validation purposes. Can this be clarified? **Proposed change (if any):**	
9.5		**Comment:** Aligns with draft guidance on setting health based exposure limits. **Proposed change (if any):** Limits for the carry-over of product residues should be based on **a scientific rationale.**	
9.5 and 9.8		**Comment:** It should be addressed how multipurpose companies which manufacture pharmaceuticals as well as food supplements should manage the PDE approachin case no PDE is available for the food supplement **Proposed change (if any):**	
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):** In a worst case approach an alternative product may be selected for cleaning validation purposes, simulating the toxic	

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		/ hazardous product.	
11.6		**Comment:** The sentence is not clear.It is to be clarified or deleted **Proposed change (if any):**	
		Comment: **Proposed change (if any):**	

Please add more rows if needed.