Volume 4
The Rules Governing Medicinal Products in the European Union
Annex 15: Qualification and Validation

Comments on the Proposed Text – Published 6th February 2014

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Review Date	Document under Review
21/05/2014	GMP Annex 15

Clause/ Subclause	Type of comment	COMMENTS	PROPOSED CHANGE	JUSTIFICATION
Principle	Ed	Spelling – 'manufacturer's'	Change to 'manufacturers'	
General	Ed	The sentence 'The principles in ICH Q8, Q9, Q10 and Q11 or other systems guaranteeing at least the same level of product quality and security should be used to support validation and qualification activities.' is unclear and would be better split into two separate statements to make the intent more clear.	Change the sentence to : The principles in ICH Q8, Q9, Q10 and Q11 should be used to support validation and qualification activities. Other systems that provide at least the same level of product quality and security may be used.	Improved clarity
1.4	Ge	Clause 1.4 makes reference to the site validation programme. The use of the word 'Programme' was felt to be a preferential term rather than the term 'Plan' that is used extensively throughout the document.	Consider changing the emphasis throughout the document to the 'validation master programme' (VMP).	The term programme infers a more definite timeframe to the validation activities.
1.5	Ge	The sentence 'The VMP should be a summary document which is brief, concise, clear and contain data on at least the following:' suggests that the information required should be repeated in each VMP, where it may already be present in documents of the Quality Management System – where it will be subject to routine revision and control.	To avoid having duplication within the various systems on site, change the sentence to: '…contain at least the following, or reference where the information can be found within the Quality Management System (QMS)'	Prevents duplication of requirements and avoids information not being updated.

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1.5	GE	The opening sentence references the 'VMP', where as Clause 1.4 defines 'VMP or equivalent document'	Change the reference in 1.5 to: 'This document should be a summary document' or 'The VMP or equivalent document should be a summary document'	Consistency with Clause 1.4
1.5f	Ed	Change control and Deviation Management for Validation" are two separate processes It would be better to refer to them as separate bullet points.	Change the bullet list to f Change control g Deviation management for validation This will impact the numbering within the clause	Improved clarity
1.5k	Ed	This subclause is written in the past tense whereas the other points are in future tense (as they refer to what has to be done). The clause has two full stops.	Change the sentence to: k confirmation that the materials to be used for validation……	Correct tense
1.6	Ge	If a separate VMP is required for large projects on site, this could again lead to unnecessary duplication within the documentation. It is proposed to suggest a separate Validation Programme which could cross reference the 'common' sections from the QMS.	Change the wording to: … a separate validation program.	Avoids duplication of common procedures.
1.7		The first sentence in the clause is difficult to understand. It would be better to rearrange the sentence so that the information is more easily understood.	Change the text of Clause 1.7 to: A quality risk management approach should be used for all validation activities. In the light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated as required. The way in which……	Improved clarity
2.1		This is an unnecessary addition, as it is a requirement of the EU GMP Guide	Delete Clause 2.1 This will affect clause numbering in Section 2	Repetition.

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2.2		Making reference to the appropriate personnel within the pharmaceutical management system contradicts the requirement specified in Clause 1.5b. The references within the Annex should be consistent. It may be better to change the reference in Clause 1.5b in line with this requirement.	Change to: All documents generated during validation should be approved and authorised by the appropriate personnel as defined in the VMP.	Consistency with other clauses
2.6	Te	Reference should be made to the deviation being approved.	Change the sentence to: …during execution should be documented, scientifically justified, and approved as a deviation.	Need to reference approval.
3.4	Ed	The sentence can be construed as a requiring all equipment to be evaluated at the vendor's site, whether it is novel or complex, or not.	Change the sentence to: If equipment incorporates novel or complex technology, it should be evaluated at the vendor prior to delivery. Other equipment may be evaluated at the factory if the risk assessment identifies the requirement.	Improved clarity
3.5	Ed	If the changes are made to Clause 3.4 this Clause becomes superfluous	Delete the Clause (assuming changes to 3.4 are agreed)	Improved clarity
3.7	Te	This Clause should also note the requirements for the addition SAT as defined in the risk assessment.	Change the sentence to: Risk assessment should be used to determine whether there is a need to supplement the FAT with a SAT. This may be revised after the equipment has been received at the manufacturing site.	Improved clarity
3.9a	Ed	Sentence difficult to understand/confusing wording	Change the sentence to: Installation of equipment, pipe work, services and instrumentation as detailed in the design drawings and specifications, including the materials of construction.	Improved clarity and adds reference to materials of construction as part of the equipment specification.
3.9b	Ed	Ambiguous use of the word 'installation'	Change the sentence to: Verification that the equipment has been installed against the pre-defined criteria.	Improved clarity
3.9e	Ed	The Clause can be deleted if the changes are made to Clause 3.9a.	Remove Clause 3.9e as the materials of construction are in intrinsic part of the specification detailed in 3.9a	Improved clarity

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3.10	Ed	As the two requirements in Clause 3.10 are quite different, the second paragraph should be separately numbered as 3.11. This will require the Clauses 3.11 to 3.14 to be renumbered.	Change Clause to: 3.10 QP normally follows……. 3.11 OQ could include but is not be limited to the following:…….	Improved clarity
3.14b	Ed	This Clause is confusing. It is not possible to fully understand the meaning of the statement. Specifically, the statement 'confirm the operational ranges are available' is unclear.	Possible change to the Clause as follows: Tests should cover the operating range: – as defined in the Design Specification or – as modified and approved during the development phases of the programme.	Improved clarity
4.2	Ed	There are too many uses of the terms 'note' or 'it should be noted'. It would be more clear if two extra clauses were added to this section of the Annex.	Split Clause 4.2 into the following: 4.2 This section should be used in conjunction with the current EMA guidelines on Process Validation, which is intended to provide guidance on the information and data to be provided in regulatory submissions. 4.3 The GMP requirements for Process Validation continue through the lifecycle of the process. 4.4 A lifecycle approach should be applied to: - linking product and process development - validation of the commercial manufacturing process - maintenance of the process in a state of control during routine commercial production.	Improve clarity.
4.3		The first sentence is too long, making it difficult to understand. In the third sentence there is no need for the phrase 'prior to marketing the product' as this is implicit in the term 'prospective'.	Change the Clause to: Medicinal products may be developed using a traditional approach or a continuous verification approach. Irrespective of the approach used, processes must be shown to be robust to ensure a consistent product quality before any product is released to the market. Manufacturing processes should undergo a prospective validation programme, wherever possible.	Improved clarity

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4.4	Ed	The first sentence is too long, making it difficult to understand. It may be more appropriate to display this information as three separate clauses with this section.	Change the Clause to: Process validation for new products should cover all intended marketed strengths and sites of manufacture. The number of validation batches could be reduced by the use of a bracketing approach for products where: - they are transferred from one site to another - they are transferred within the same site, - there is existing product knowledge, including the content of the previous validation. Different strengths, batch sizes, pack sizes and container types may also use the bracketing approach where it can be justified by a documented risk assessment.	Improved clarity
4.20e/ 4.20f	Ed	These two references should be a single reference.	Change Clause to : e) List of the equipment/facilities to be used (including measuring/monitoring/ recording equipment) together with the calibration status f) List of analytical… all subsequent line numbering to be changed	Correction
4.24	Ed	The second sentence is too long, making it difficult to understand.	Change Clause to: A hybrid of the traditional approach to process validation and continuous process verification may also be used as an approach to validation activities where the following can be demonstrated: - Significant documented product and process knowledge - An understanding which has been gained from manufacturing experience - Historical batch data. This approach may be adopted for any validation activities after changes to the process or during ongoing process verification even though the product was initially validated using a traditional approach.	Improved clarity

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4.26	Ed	The sentence requires rephrasing to make it more clear.	Change Clause to: The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements, taking into account the current level of process understanding and process performance.	Improved clarity
4.27	Ed	Typographical error: on going is a single word. Also applies to Clause 4.28 and 4.29	Change Clause to: Ongoing process verification……..	Correction
4.28	Ed	The first sentence is too long, making it difficult to understand.	Change Clause to: Ongoing process verification should be used to support the validated status of the product in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, such as enhanced sampling, should be assessed.	Improved clarity
4.29	Ed	Need to clarify the term 'could have an impact' possibly by introducing a reference to risk assessment.	Change Clause to: Ongoing process verification should be considered where any individual change or successive incremental changes during the product lifecycle could have an impact on the validated status of the process. This may be identified by trend analysis and/or risk assessment.	Improved clarity
5.2	Te	Seasonal is not the only consideration that should be made when considering transport.	Change Clause to: …transport across continents, seasonal and environmental variations should also be considered.	Improved clarity
6.1	Te	This clause is too prescriptive. It is suggested that all changes to primary packaging require validation	Change Clause to: Primary packaging processes should undergo validation where risk assessment identifies that the variation in the equipment processing parameters during primary packaging may have a significant impact of the integrity and correct functioning of the pack.	Adding the requirement for risk assessment to identify whether there is a need for package revalidation.

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7.1	Te	This clause appears to be too prescriptive. Risk assessment should be used to identify the requirement for validating the utilities, based on whether they come into contact with the product during the manufacturing process.	Change Clause to : Where identified by risk assessment, the quality of the utilities used (including steam, water, air, other inert gases and coolants) should be confirmed following installation, using the qualification steps described in section 3.	Use of risk assessment to identify the need for validation of utilities.
7.2	Ed	Redundant use of the word 'also'	Change Clause to: The period and extent of the utility qualification should reflect its intended use any relevant seasonal variations.	Improved clarity
7.3	ed	The requirement for validation ois unclear in the statement..	Change Clause to: Where a risk assessment has identified a potential risk of direct contact of utilities with the product, the mitigation to cover the risk of failure should be validated.	Improved clarity
9.1	Te	Too prescriptive. Suggests all equipment must undergo cleaning validation	Change Clause to: "Cleaning validation should be performed where the necessity for equipment cleaning is identified through risk assessment. The validation should be completed in order to confirm the effectiveness of any cleaning procedure. Where different……	Improved clarity
10.2	Ed	Remove 'additionally' as it is redundant. Remove space between 're-' and 'qualification'	Change Clause to: Where re-qualification is necessary…	Correction
11.1	Ed	Change the wording to 'change control' to reflect correct terminology	Change to Clause to: Change control is an important…	Rewording
11.2	Ed	To make the clause easier to understand, change to list to a bullet list.	Change Clause to: Written procedures should be in place to describe actions to be taken for any planned changes including: - starting materials, - product components, - processes, - equipment, - premises.	Improved clarity.

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11.6	Ed	Demonstrated is not an appropriate word to use.	Change Clause to: Supporting data should be generated to confirm that the impact of the change has been evaluated prior to approval.	Improved clarity
Glossary Change Control	Te	The definition used is too narrow and should be broadened to cover the scope of Change Control for all QMS activities.		