2 June 2014

Submission of comments on:
Revision of EU Commission guidelines on GMP for Medicinal Products:
Revision of Annex 15 – Qualification and Validation

Comments from:

Name of organisation or individual
AESGP

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	AESGP appreciates the opportunity to provide comments on this revised guideline. We welcome the inclusion of life-cycle concepts of process validation which brings some level of harmonisation with other issued and draft guidance documents available. Reference to bracketing is appreciated but the guideline would benefit from the risk-based approach to more generally drive the requirements. We believe that further clarity is required as to overall scope of the Annex and how it aligns with the QWP guideline on Process Validation. Clarification of important terminology used in the Annex is also required. Greater alignment with the US FDA guideline on Process Validation should be considered. Application of the Annex to equipment used in the development lifecycle would be helpful i.e. equipment may not need to be 'fully validated', but should be qualified and fit for purpose. With regard to the toxicological approach (PDE), we	

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	believe that it should not be automatically applicable to all substances/products.	

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		Comment/Proposed Change (if any): We recommend that ICH Q9 is included as a reference in this section.	
Section 1.3		Comment: It should be clarified that Quality oversight of Validation activity should be in place. Proposed Change (if any): "Validation personnel 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 appropriate quality oversight over the whole validation life cycle."	
Section 1.5		Comment: The proposed content of the validation master plan (VMP) is too wide and should be limited to what is really necessary to be consistent with the aim of having a VMP which is "brief, concise and clear". Proposed change: remove c), d), i) and k)	

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Section 1.6		Comment: One VMP should be the rule. In rare cases however we acknowledge that a separate VMP may be needed. Proposed change: Please reword to make it clear that this would be an exception.	
Section 1.7		Comment: As change control is a primary driver to the maintenance of Validation status, Quality Risk Assessment should be applied to the change control operation as well as during Process Validation. Proposed Change (if any): "The way in which risk assessments are used to support change control and validation activity should be clearly documented."	
Section 2.5		Comment: Further clarity on the use of Vendor protocols would aid utilisation of the principle. Proposed change (if any): "The manufacturer should evaluate third party (Vendor)	

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		protocols for suitability and compliance with company procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols, to ensure testing objectives are met.”	
Section 2.6		Comment: Some changes to approved protocols may be self-evident, and not require documentation as a deviation. Proposed change (if any): “Any changes to the approved protocol during execution should be documented and justified.”	
Section 2.9		Comment: This section requires an approved validation report or a separate summary document to move from one step in the qualification process to another. In many cases an approved test protocol, with a summary statement would fulfil the requirement without creating a separate document. Proposed change (if any): Consider replacing the first sentence with the old content “After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.”	

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Section 3.1		Comment: Subchapter 3.1 starts "Validation and qualification activities should consider …". However, equipment, facilities etc. are qualified, not validated (see also the title of this Chapter). Proposed Change (if any): "~~Validation and~~ Qualification activities should consider …".	
Sections 3.4 to 3.7 – Factory acceptance testing (FAT)		Comment: We welcome the possibility for a FAT (sections 3.4 and 3.5). However, whether a FAT is necessary depends on the complexity of the equipment and the extent of customer adaptions to standard equipment. Proposed Change (if any): We propose to add in section 3.4 a second sentence, that reads "Need and scope should be determined following a risk-based approach."	
Section 3.9, 3.10 & 3.14		Comment: Typographical errors in the introductory sentences of these sections: Proposed change (if any): Delete "be", to read "... could include, but is not limited to the	

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		following:"	
Section 3.9a		Comment: The sub bullets need context as to the purpose of IQ testing. Proposed change (if any): "Verification of correct installation of equipment, pipe work, services and instrumentation as detailed in the design and confirmation of current engineering ~~regarding~~ drawings and specifications."	
Sections 3.10 & 3.11 – Operational qualification (OQ)		Comment: For clarification, we propose to add at the end of section 3.11 the following sentence, which is the second sentence of no. 15 of current Annex 15 from 2001: "It should permit a formal release of the facility systems and equipment." Proposed Change (if any): "3.11 The completion of a successful ... requirements. It should permit a formal "release" of the facilities, systems and equipment."	
Section 3.10a		Comment: This statement does not give any indication of the purpose of the testing to be undertaken, or that product knowledge will	

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		dictate criticality of devices. Proposed change (if any): "Tests that have been developed from ~~the~~ knowledge of the product, processes, systems and equipment to ensure the system is operating as designed and specified."	
Section 3.14		Comment: A risk-based (bracketing) approach to PQ testing should be allowed for systems that handle large combinations of components, such as secondary packaging equipment. Proposed change: Revise text to: a) Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions and across the intended batch size range. The sampling strategy used to confirm process control should be justified. b) Tests should cover the intended operating range of the process. Documented evidence from the development phases which confirm the operational ranges may be used. Add as a new bullet item "c) A bracketing approach may be used to optimise the testing plan."	

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Section 4.3		Comment: This section uses the term continuous verification, which is inappropriate as a description of product design. Proposed change (if any): "irrespective of the approach used to develop a medicinal product, processes must be shown to be robust and ensure consistent product quality before any product is released to the market."	
Section 4.9		Comment: For legacy products, the recent manufacturing history is potentially more relevant than the initial development data. To take account of changes made during the commercial life of the product. Proposed change (if any): "For all new products irrespective of the approach to product development used, process knowledge from development studies should be accessible to the manufacturing site, ~~unless otherwise justified~~, and be the basis for validation activities. For the revalidation of existing products/processes accumulated manufacturing history would be more relevant."	

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Section 4.10		Comment: The list of personnel involved is potentially not representative of all situations. To remove this shortfall suggest the first sentence is deleted, to concentrate on the mandated requirement that personnel are 'trained' Proposed change (if any): "For process validation~~, batches, production, development, or other site transfer personnel may be involved. B~~batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding when commercial manufacture starts"	
Section 4.14		Comment: The assessment of patient risk-benefit is subject to management decision making process. Proposed change: Revise accordingly, removing the words "where there is a strong risk benefit to the patient".	
Section 4.19		Comment: First introduction of the terms CQA and CPP.	

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		Proposed change (if any): It would be better to introduce these terms earlier in the section e.g. around section 4.3/4.4 to indicate that one of the output of product development is knowledge/clarity of CQAs and CPPs to be controlled during Process Validation.	
Section 4.20		Comment: Bullet point f) is in fact a continuation of bullet point e) Proposed change (if any): Merge the two bullets points.	
Section 4.21		Comment: This section would benefit from some clarification around the role of control strategy within the concept of continuous process verification. The use of the phrase 'routine process control' makes the elements sound very traditional and could lead to misinterpretation of the desired outcome. Proposed change (if any): "For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional	

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		process validation."	
Section 4.22		Comment: The construct 'process verification system' is misleading. Proposed change (if any): "The method by which process will be verified should be defined and there should be a science and risk based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation."	
Sections 4.25 to 4.29		Comment: The introduction of a stage that verifies the continued capability of the validated control strategy is welcomed. It would be helpful if consistent terminology with the US FDA PV guidance and other draft documents for the purpose of harmonisation e.g. Continued Process Verification	
Section 5.3		Comment: The text should not cover the factors which are already covered by product specification and that of its primary packaging. Proposed change:	

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		We suggest to reword as follows: "a risk-assessment should be performed to consider the impact of variables in the transportation process, other than those conditions which are continuously controlled and monitored, …"	
Section 7.1		Comment: The risk-based approach should be taken into account here. "coolants" should be removed as not in direct contact with the product. Proposed change: Please reword as follows: "When justified by product risk assessment, the quality of steam, water, air, other inert gases, etc."	
Section 9.2		Comment: The draft states that a visual check for cleanliness is not acceptable for this criterion alone to be used. A visual check (visually clean) is not an acceptance criterion in the strict sense but constitutes a detection method which is able to recognize substances on stainless steel surfaces – when visually inspected. Diverse investigations revealed, that pharmaceutical solids can be visually recognized, starting with concentration of 4µg/cm^2 (see references a) through below).	

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		Proposed Change (if any): Replace the existing by the following wording: "9.2 A visual check (visually clean) is a detection method to verify the acceptance criterion selected (e.g. 10 ppm). The method can be used when the visibility limits for the group of substances in question are known, demonstrated either by literature or own investigations." References: a) Fourman, G.L. and Mullen, M.V., „Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations", Pharm. Technol. 17(4), 54-60 (1993). b) Buscalferri et al., „Reinigungsvalidierung – Bestimmung der Sichtbarkeitsgrenzen von pharmazeutischen Feststoffen auf Edelstahloberflächen", Pharm. Ind. 62(6), 411-414 (2000); und Erratum, Pharm. Ind. 62(11), 840 (2000). Determination of visibility limits of pharmaceutical solid materials on stainless steel surfaces. c) Wollenweber et al., „Methoden zur Bestimmung der Nachweisgrenze pflanzlicher Urtinkturen auf Edelstahloberflächen", Pharm. Ind. 64(8), 816-821 (2002).	

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		Methods on determination of the detection limit of mother tinctures of plant origin on stainless steel surfaces.	
Section 9.5		Comment: The carry over of product residues should be avoided for all products by appropriate cleaning of the equipment used. The current approach to meet this requirement is to reduce the concentration of residual active substance to a level not greater than 1/1000th of the lowest clinical dose (1/1000th dose criterion). This is the main acceptance criterion from the pharmacological-toxicological point of view. Only in cases where the dose criterion is not applicable, (e.g. topical application) the so called 10 ppm criterion is used. The present draft Annex 15 requires that the product specific permitted daily exposure (PDE) value provides the limit for the carry over of product residues. This approach is too restrictive as it only indicates the use of PDE. Proposed Change (if any): Please reword as follows "Limits for the carry over of product residues should be no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product to be manufactured. When this criterion is not	

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		applicable the maximum permitted carry over is 10 ppm of the previous active substance in the next product manufactured."	
Section 9.7		Comment: Time and number of batches are not always equally important to ensure the cleanability or detectability of product residues after campaigns. Proposed change: Please reword as follows: "the maximum length of a campaign (in time and/or number of batches) should be …."	
Section 11.6 & 11.7		Comment: "Supporting data should be generated", "An evaluation of the effectiveness of change" Proposed change (if any): These sections should be linked to the currently named Ongoing Process Verification, as the monitoring and trending of that lifecycle stage will help confirm that changes have been successful, or have had no impact on the control strategy.	
Glossary		Comment: The difference between verification and validation is not	

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		widely well understood, partially because the terms are often used interchangeably. Proposed change (if any): Consider adding definitions for Verification and Validation, to differentiate between the two concepts. Verification being a one off event that demonstrates compliance with an acceptance criterion, whilst validation is a demonstration that the process is capable of routinely achieving compliance with criterion.	
Glossary		We suggest including a definition of the general terms "Qualification" and "validation". Cleaning validation The removing of **all** traces of the previous product as stated in the revised version doesn`t describe the reality. For reason of clarification we propose to remain the current definition, which reads "Cleaning validation is documented evidence that an approved cleaning procedure has removed residues to a level which is suitable for further pharmaceutical processing".	