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May 29, 2014

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

Ref: EudraLex Volume 4 EU Guidelines for GMP Annex 15: Qualification and Validation

Dear Sir/Madam,

PDA welcomes this extensive revision of Annex 15 to align with Chapter 1 of EU Volume 4, Annex 11, and ICH Q8 – 11. The revised Annex 15 is a positive adaptation to current knowledge and technology. There is flexibility in designing the qualification, validation and technology transfer plans and acceptance criteria, based on previous knowledge, experience, and risk assessments. PDA appreciates that this draft provides for both the traditional approaches and newer QbD approaches.

PDA recognizes that not all readers of this guidance are experienced in process validation concepts and PDA would like to offer suggestions for further clarification and details regarding requirements. PDA also believes that this Annex should not be too prescriptive but should be written to allow other established methods and has provided specific comments below on this aspect.

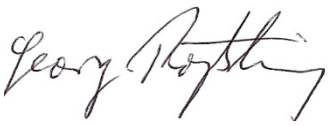
PDA appreciates the sentiment expressed in the Annex that it is the careful evaluation of data and risk based understanding of the process variables which result in effective process control and validation, rather than the mere running of replicate batches. To that end, PDA is concerned that the reference to a specific minimum number of batches (in this case three) needed to validate the process will lead some companies to incorrectly forego the efforts to develop this process understanding. Some firms will opt instead for running three batches without the applying principles of quality risk management, including planned data evaluation and justification, thus negating the best intentions of the Annex. For that reason, PDA recommends removing the reference to three batches, or any number, and instead reinforcing the evaluation of data and determination of number of batches needed to provide that data.

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 validation representing our Board of Directors, our Science 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.
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Attachment

<28 May 2014>

Submission of comments on EU GMP Annex 15: Qualification and Validation

Comments from:

PDA (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).

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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)*
	PDA welcomes this extensive revision to align with Chapter 1, Annex 11, ICH Q8 – 11. The new annex is a positive adaptation to the current knowledge and technology. There is more flexibility in designing the qualification, validation and technology transfer plans and acceptance criteria, based on previous knowledge, experience, and risk assessments. PDA appreciates that this draft provides for both the traditional approaches and newer QbD approaches. PDA recognizes that not all readers of this guidance are experienced in process validation concepts and PDA would like to offer suggestions for further clarification and details regarding requirements. PDA also believes that this annex should not be too prescriptive but should be written to allow other established methods and has provided specific comments below on this aspect.	
	PDA recommends including a definition of both Validation and Qualification, such as the definitions from ICH Q7, in this Annex to avoid ambiguity and confusion. PDA understands the term “validation” to encompass the life cycle approach and “qualification” to apply to the the separate activities in the validation process and has included suggested definitions in our specific comments below. PDA further recommends the term “Qualification” applies to supporting systems and processes such as Utilities (section 7) and Transportation (section 5) and the term Validation be applied to the manufacturing process and analytical methods. In keeping with current thinking about lifecycle process validation, PDA also recommends adding that concept to the end of the Q7 definition of validation as noted below. Qualification: *Action of proving and documenting that equipment or ancillary systems are*	

	properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. Validation: *A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria* ***throughout the lifecycle.***	

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 (if applicable) *(To be completed by the Agency)*
Para 1.3		Comment: The meaning of this section of text is unclear: "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 oversight over the whole validation life cycle." This sentence seems redundant with quality system requirements which govern all personnel roles and responsibilities. Proposed change (if any): PDA proposes to delete the item 1.3.	
Para. 1.5		Comment: Clarification of wording is needed. For example, "contain data" is not the right wording because many of the items listed in the following paragraphs are not data. In addition, Validation strategy of the particular project or process undergoing validation is more appropriate to a VMP than high level policy. The firm's validation policy should be stated as part of the overall Pharmaceutical Quality System not as part of an individual VMP. Proposed Change: The VMP should be a summary document which is brief, concise, clear, and contains ~~data~~ **information and references** on at least the following: (a) Validation ~~policy~~ **strategy**	
Para 2.4		Comment: PDA recommends adding clarification that the term critical be applied to attributes and parameters not systems as it is used in ICH Q7. Proposed Change: …protocol should be prepared which defines the critical ~~**systems**~~ attributes and parameters **for facilities, systems or equipment, which are important** and the acceptance criteria for each.	

Para 2.9		Comment: PDA agrees with the requirement for formal release between validation steps but recommends being less prescriptive about how the release is documented. Proposed Change: A formal release for the next step in the validation process should be authorized **and documented** by the relevant responsible personnel. ~~as part of the validation report approval or as a separate summary document~~.	
Section 3		Comment: PDA recommends the Annex provide specific definitions for Qualification and Validation in section 3 as well as the glossary. We suggest ICH definitions from IQ7 with a slight modification to include lifecycle concepts to bring the definition up to date. Proposed Change: PDA recommended definitions listed in our comments to the general section above and the glossary section below be added to section 3.	
Para 3.4 and 3.5		Comment: Requirements to complete equipment evaluation at vendor site prior to delivery are business decisions and it would be overly burdensome to make these regulatory requirements. In the case of off the shelf equipment (e.g. a lab pH meter), FAT/SAT are unreasonable and not current practice. Proposed change: PDA recommends deleting current text in paragraphs 3.4 and 3.5 and replacing with the following: **Manufacturer should confirm equipment meets URS and functional specification prior to qualification**. **This may be completed during FAT or SAT or provided by the vendor for off the shelf equipment.** Test results from FAT/may be used for IQ/OQ if equivalent to tests foreseen during those phases.	
Para 3.9(e)		Comment: PDA recommends verification should not be applied for all materials of construction, just for those which may have an impact on product, process or function. Proposed change: Verification of materials of construction, **as appropriate.**	
3.11		Comment: In PDA's experience, procedures covering cleaning are typically not finalized at the OQ stage because product is not generally introduced at this stage. Proposed change: The completion of a successful OQ should allow the finalisation of maintenance plans, standard operating ~~and cleaning~~ procedures, operator training and preventative maintenance requirements.	

Para 3.14 (a)		Comment: PDA agrees that operating conditions should be included in testing but worst case batch sizes can be used on production scale equipment only and are thus are too specific for some necessary PQ activities. Proposed change: Tests **to confirm that the equipment performs as intended under representative operating conditions** using production materials, qualified substitutes, or simulated product proven to have equivalent behavior. ~~under normal operating conditions with worst case batch sizes.~~ The **testing conditions and** frequency of sampling ~~used to confirm process control~~ should be justified.	
Para 3.14 (b)		Comment: PDA is concerned this sentence may be mis-interpreted and suggests re-wording to clarify intent is that PQ is only needed in normal operating ranges not at extremes. Proposed Change: Tests should cover the operating range of the intended process. ~~unless~~ **If** documented evidence from the development phases ~~which confirm~~ **supports** the operational ranges, ~~are available~~, **then PQ can be performed at the set point.**	
Para. 4.3		Comment: It is not clear what is meant by a "continuous verification approach" to development. The glossary definition is related to process validation and not product development. "Traditional" is used in different ways applying to development and product validation. Other strategies such as "enhanced" or "QbD" are also used for product development. To clarify and allow for a variety of approaches, PDA recommends using a more general and inclusive term. Proposed change (if any): Medicinal products may be developed using a ~~traditional approach or a continuous verification approach~~ **number of approaches** however**…**	
Para 4.4		Comment: A bracketing strategy should also be applicable to new products where development data supports no differences among strengths of a common blend, and the process is robust with respect to blending and impact of batch sizes. Proposed change (if any): Process validation for new products should cover all intended marketed strengths and sites of manufacture. **The number of validation batches can be reduced by the use of a bracketing approach.** ~~However~~, **Additionally this could also apply** for products which are transferred…	

Para 4.8		Comment: The statement "Test Methods should be validated." does not take into account the lifecycle approach to validation where methods may not be validated in early developmental stages in the process. PDA recommends use of language from Technical Report #60, *Process Validation: A Lifecycle Approach*, section 4.2.1. (This language is also appropriate for paragraph 8.1 See additional comment below.) Proposed change (if any): …and test methods should be **appropriately** validated **or suitably qualified and their status documented.**	
Para. 4.17		Comment: A small number of batches (e.g. 3-5) can never sufficiently explore the potential range of variation or provide sufficient data to understand process trends. In fact, assessing variability and process trending is the purpose of performing ongoing process verification (a.k.a. process performance monitoring). As it is described in the draft, understanding variation and trends is not an appropriate basis for justifying the number of validation batches. Proposed change (if any): Each manufacturer must determine **the data required** and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product. **The number of batches manufactured and the number of samples taken should be based on quality risk management principles,** ~~allow the normal range of variation and trends to be established and provide sufficient data for evaluation.~~ **and represent the normal range of variation supported by sufficient data.**	
4.18		Comment: PDA Recommends deleting 4.18 because specifying three batches is unnecessary if QRM principles noted in 4.17 are followed. PDA feels that if the annex continues to refer to a specific number of batches some firms will continue to use that as default and not perform the needed analysis to determine a more appropriate approach. Proposed Change: Delete 4.18	
4.20		Comment: Not all GMP information should need to be repeated in the validation protocol. PDA believes redundant information in several documents poses the risk for inconsistency, which can be minimized by making references. Proposed change: Add the following sentence: **If content is described in other GMP documentation, reference to those documents can be made.**	

Para 4.20 (d)		Comment: PDA recommends that any attributes or parameters that are investigated or monitored during validation should be included and summarized in the validation protocols. This listing in (d) seems redundant with (h), (i), and (j). Proposed Change: PDA recommends moving (d) to following (j) in the list of items.	
Para 4.22		Comment: PDA agrees with the concept of a science based control strategy but recommends avoiding the terminology "number of batches" to allow for future flexibility in the document. Proposed Change: Each manufacturer must determine and justify the ~~number of batches~~ **amount of data** necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.	
Para 4.24		Comment: Is there a difference intended between "continuous process verification" and "continuous verification"? PDA recommends adding "process" back into the second sentence of the paragraph for clarification. Proposed Change: …and historical batch data, continuous **process** verification may also be used…	
Para. 4.27		Comment: The use of an approved protocol for ongoing process verification is too restrictive – there may be other ways of achieving this, such as using a plan or SOP. This permits modifications in criteria as process data is accumulated and process capability is demonstrated over time as noted in 4.26. Proposed change (if any): Ongoing process verification should be conducted ~~under~~ **using** an approved protocol**, plan, or procedure** and a corresponding report should be prepared **periodically** to document the results obtained…"	
Para. 5.4		Comment: PDA recommends that the degree of environmental monitoring should be risk-based and adding a sentence to this effect. Proposed change (if any): …should be performed. **The degree of monitoring may be determined based upon the risk assessment performed.**	

Para 8.1		Comment: Methods should be reliable and fit for purpose but the extent of validation should be commensurate with the phase of product development as discussed in PDA Technical Report #60 *Process Validation: A Lifecycle Approach*. (See similar comment to paragraph 4.8) Proposed Change: All analytical test methods used in qualification, validation or cleaning exercises should be **appropriately** validated **or suitably qualified** with an appropriate detection and quantification limit.	
Para 9.2		Comment: Visual inspection is commonly used to check effectiveness of routine cleaning operations. PDA recommends clarification that 9.2 is in reference to validation activities and not to ongoing production. Proposed change (if any): Repeated cleaning "until clean" is also not considered an acceptable ~~approach~~ **alternative to cleaning validation.**	
Para 9.5		Comment: To better align with current industry practices, PDA recommends reference to published guidance on setting cleaning limits as defined in ICH Q7. Proposed change (if any): Limits for the carryover of product residues should be **practical, achievable, verifiable, and** based on **the most deleterious residue. Limits should be established by considering risk to patient safety using a** toxicological evaluation **(*e.g. Permissible Daily Exposure,* Acceptable Daily Exposure,)** ….	
Para 9.7		Comment: Process and product residues vary and the impact on campaign length with respect to time and carry-over between batches is process specific. PDA recommends that either time or number of batches and not both may be not appropriate. Proposed change (if any): Revise text to state …"maximum length of a campaign (in ~~both~~ time **and / or** number of batches) should be the basis …	

Para 9.10		Comment: PDA proposes clarification to this paragraph by moving the statement on recovery so that it is clearly applicable to swab testing. Proposed change (if any): … The swab materials should not influence the result. **Recovery should be shown to be possible from all materials that are swabbed.** If rinse methods are used…. cleaning procedure. ~~Recovery should be shown to be possible from all materials used in the equipment with all sampling methods used.~~	
Para 9.12		Comment: Cleaning verification is not defined in this guidance. PDA recommends that expectations should be defined or reference to a definition be provided, such as PDA Technical Report #29 *Points to Consider for Cleaning Validation*. Proposed change: Add the following to the glossary: **Cleaning Verification:** **A one time sampling and testing to ensure that specified equipment has been properly cleaned following a specific cleaning event.**	
Glossary: Cleaning Validation		Comment: PDA recommends modification to the definition of cleaning validation because it is not feasible or measureable to remove all traces of the previous product and proposes using a definition similar to previous version. Proposed change: Cleaning validation is documented evidence that an approved cleaning procedure will remove ~~all traces~~ **residues** of the previous product used in the equipment **to a safe and acceptable level**.	
Glossary: Knowledge Management		Comment: PDA recommends using the entire definition from ICH Q10 and adding the reference. Proposed change (if any): A systematic approach to acquire, analyze, store and disseminate information **related to products, manufacturing processes and components. (ICH Q10)**	

Glossary: Qualification		Comment: PDA recommends adding the definitions of qualification and validation from Q7 with the addition of lifecycle concepts as noted below. See also PDA's general comments. Proposed Change: Qualification: *Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation. (ICH Q7)*	
Glossary: Validation		Comment: PDA recommends adding the definitions of qualification and validation from Q7 with the addition of lifecycle concepts as noted below. See also PDA's general comments. Proposed Change: Validation: *A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria* ***throughout the lifecycle.***	

Please add more rows if needed.