Submission of comments to: Revision of EU GMP Annex 15: Qualification and Validation

http://ec.europa.eu/health/files/gmp/2014-02_pc_draft_gmp_annex.pdf

Comments from: LEEM

Name of organisation or individual

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)*
	LEEM welcome the revision of Annex 15 "Qualification and Validation" of *the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* to reflect the current and state-of-the-art guidance impacting process validation, as well as the use of QRM and reference to latest ICH guidance , however some of the detail is too prescriptive to allow other established accepted methods, new methods or emerging technology to be fully utilised. **LEEM appreciate the opportunity to comment, we**	

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	believe that the document is well written and structured. In especially, we appreciate the approach to take into account current requirements of ICH Q8, Q9, Q10, Q11 and the QWP Guidance on Process Validation. However, our review of the document revealed some general and specific comments which we would like to highlight with request for consideration upon finalisation of the draft document. **There is an increase level of details that are described in this Annex 15 revision draft, where the current annex is a 5 pages length description of the expectations. This version is now a 17 pages description with a lot of details/suggestions that go beyond the spirit of GMPs. In parallel of this revision, the Guideline EMA/MHMP/CVMP/QWP/70278/2012-rev1. Has just been published and should match (1) in scope and (2) intent. The Guideline is a shorter description of 11 pages.** **GMPs are legally opposable and should not substitute their content with the intent of the Guidelines. Further to this, at time of globalization, there is a need for harmonization with the current applicable US Guideline, titled "Process validation – General principles and practices applicable since January 2011. As such**	

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	EU GMP annex 15 and Guideline on Process validation should merge into only one type document and shall consider more clearly international references. **The intent of validation starts with ICH Q8 leading to define what will be evaluated and chosen for validation. The second element is set in the recently adopted guideline. Annex 15 shall not reproduce what has been evaluated at the 2 precedent steps, rather gives a high level practical expectation.** **A typical illustration is with paragraph 1.5 which goes to the details of the VMP summary. GMPs shall keep flexibility into its approach and not list summaries of document contents.** **The document makes frequent reference to the use of risk assessment, even when risk assessment that all the references to risk assessment in the document are replaced with the term "documented rationale" which could be a risk assessment or other scientific rationale.** **Throughout the document, terminology on Qualification and Validation appears to be not**	

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	harmonized, for example "All qualification and validation activities" (1.1), "Validation activities" (1.2), "Validation and qualification activities" (3.1). Proposal to harmonise language to "qualification and validation activities" (in this order). **Throughout the document, terminology on Facilities, Utilities, Equipment and Systems appears to be not harmonized. For example "facilities, equipment, utilities and processes" (principle), "facilities, systems or equipment" (3.2. and 3.3), "facilities, systems and equipment" (3.8), "facilities, systems, utilities and equipment" (4.8). Proposal to harmonise language to "facilities, utilities, equipment and/or systems".** **The term "system" is not defined in the Glossary. is probably not the appropriate tool or approach. It is recommended.**	

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: ICH Q9 is not included in list at end of paragraph – compare to General section just below, where it is included** **Proposed change (if any): Include ICH Q9 in list at end of paragraph.**	
Para. 1.3		**1.3 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.** **PROPOSED CHANGE** **There should be quality oversight throughout the entire validation life cycle, however validation personnel do not have to report into the Quality function."**	
Para.1.5		Comment: Text says "…and contain data…", but most of the listed items do not have associated data. Proposed change: "contain data" should read "describe"	

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Para.1.5		Comment: Criteria and frequency for re-qualification (noted in Section 10) are not included in expectations for VMP. Proposed change: Add a new item that VMP should include criteria and frequency for re-qualification/re-validation	
		LEEM SYNTHESIS **Proposed change: The VMP should be a summary document which is brief, concise, clear and describe at least the following if not covered by SOPs** **a) Validation policy,** **b) The organizational structure for validation activities.** **c) Summary of the facilities, systems, equipment, processes on site and the current validation status.** **d) The on-going validation strategy, including revalidation and / requalification, where applicable** **e) Planning and scheduling. This item need to be clarify** **f) Change control and deviation management for validation,** **g) Handling of acceptance criteria : this item need to be clarify** **h) References to existing documents.**	

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Section 2.2		**Comment: The language "All documents generated during validation …" appears too general.** **Proposed change: Rephrase to "All documents generated during each step of qualification and validation …"**	
Section 2.4		**Comment: This step states, "A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important and the acceptance criteria for each." Do the acceptance criteria refer to the critical systems or just to the attributes and parameters which are important?** **Proposed change (if any): Recommend rewording statement to, "… which defines the critical systems, and the acceptance criteria for the attributes and parameters which are important."**	

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Para. 2.5		**Comment: We interpret this statement to apply to a third party performing validation services for a manufacturer. We agree with the provision described in this statement, but it should be clarified so the reader will know (s)he is understands the message correctly.** **Proposed change (if any) (changes underlined): "<u>Where a third party is providing validation services</u>, the manufacturer should confirm the suitability and compliance with company procedures before approval <u>of validation documents</u>**	
Para. 2.6		Comment: Not all departures are necessarily deviations **Proposed change (if any): "Any changes to the approved protocol during execution should be documented and scientifically justified *in accordance with a deviation management or other relevant procedure*."**	
Para. 2.7		Comment: Not all failures are necessarily the result of a deviation **Proposed change (if any): "Results which fail to meet the pre-defined acceptance criteria should be recorded *and be fully investigated in accordance with a deviation management or other relevant procedure,* and any implications for the validation discussed in the report."**	
Para 2.8		Comment: **"The conclusions of the validation should be reported**	

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		and the results obtained summarised against the acceptance criteria." **Proposed change (if any): Rephrase to read: "The conclusions of the validation, including any comments and analysis, should be reported and the results obtained summarised against the acceptance criteria."**	
Para 2.9		**Comment: The meaning of "next step in the validation process" is not clear. In section 3, the term "stages" is used. Is it required to have a formal release between each qualification stage (described in §3) or only between Qualification and Validation and Validation and Production?**	
Para 3 :		Comment: The link between FAT/SAT and IQ/OQ/PQ is not clear. The addition of FAT/SAT without further clarification introduces the need to have 5 stages FAT/SAT/IQ/OQ/PQ without added value. Proposed change (if any): A statement should be added to clarify that section 3.6 applies also to IQ/OQ and not only to SAT.	
Para 3		Comment: There is little in the sections on IQ, OQ and PQ that ties back to risk management. One of the goals of this	

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		revision is to connect to ICH guidance on risk management Proposed change (if any): Propose to add general statement prior to step 3.1 that refers to a risk based approach for any and all of the subparts of section 3.	
Para. 3.1		**Comment: There is no mention of Commissioning and Qualification or the Verification approach as currently practiced in the industry. This draft of Annex 15 does not acknowledge the progression from conventional equipment qualification to the more contemporary processes defined by both eg ISPE and ASTM and widely accepted in the industry.** **Comment: Clarify that FAT and SAT are not, strictly speaking, part of the qualification process but are recommended preliminary or complementary steps. Organization and rules applicable to qualification and listed in sections 1 and 2 may not apply to FAT/SAT, for example vendor's roles and responsibilities, documentation, deviation management will usually differ. The current structure of section 3 may lead to various interpretations.** **Proposed change (if any): It is important to include the C&Q and Verification approaches to allow the flexibility**	

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		to use these approaches. FAT and SAT support the qualification process but are not strictly part of it. As such, FAT and SAT follow specific management rules and criteria, which differ from those defined in sections 1 and 2 for qualification."	
Para 3.2		**Comment: The second sentence of this step states, "The essential elements of quality need to be built in at this stage and any GMP risks minimized." This could be brought more in line with ICH Q9 by adding additional clarity to what is meant by "minimized."** **Proposed change (if any): Suggest adding the following to the end of the sentence: "… GMP risks should be mitigated to an acceptable level."**	
Para 3.3		**Comment: The text now mandates the execution of design Qualification (DQ) in all cases, which was not the case in the current version of Annex 15. There can be cases where the elements of DQ can be confirmed in later stages of the validation and therefore a separate DQ is not required.** **Proposed change: Add at the end of section 3.3 "Part or all of the DQ requirements may be integrated into later stages of validation."**	
Para 3.3		**Comment: Since DQ should not be required for all cases,**	

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		a risk based approach including complexity and/or criticality of the system could be applied. **Proposed change: Change last sentence to read: "The requirements of the user requirement specifications should also be verified during the design qualification, especially for non-standard or complex systems."**	
Para. 3.4 to 3.7		**Comment: It should be the business that determines the most cost effective way to ensure the correct equipment is installed. Regulatory agencies should primarily care that the installed equipment meets specifications, not the process it took to reach that state.** **Proposed change (if any): suggest adding: (3.4) Equipment, esp. if incorporating novel or complex technology, *may be* evaluated at the vendor prior to delivery. (3.5) Prior to installation, equipment *may be* confirmed to comply with…**	
Para 3.9 a		Comment: The elements of the sentence should be brought into a more logical order. "Components" should be added. Proposed change: Rephrase to read: "Installation of components, instrumentation, equipment, pipe work, services as detailed in the design……"	
Para 3.14b		**PQ could include, but is not be limited to the following:**	

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		b) Tests should cover the operating range of the intended process, unless documented evidence from the development phases which confirm the operational ranges are available. **This particular point should be commensurate with the drug product development option according to ICH Q8 (traditional or design space).In the case of a design space approach, there is normally sufficient supportive information at the development stage to adjust the validation exercise where it has to be.**	
Para 4.2		**This section should be used in conjunction with the current EMA guideline on Process Validation. Note: It should be taken into account that the guideline on Process Validation is intended to provide guidance on the information and data to be provided in the regulatory submission and GMP requirements extend beyond this. It should also be noted that a lifecycle approach is applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.** **There is a need of coordination and alignment between the 2 documents. Further to this a clear line shall be clarified in both documents for what relies upon a regulatory description from what is purely of**	

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		GMP nature and NOT part of submission. Further the intent of the Annual Product Review is to evaluate what validation exercise might be necessary at the conclusion of the review. This cannot be delegated nor being outside the scope of the QP's responsibility.	
Para. 4.3		**Comment: it is not clear what is meant by a "continuous verification approach" to development. The usual alternative to the 'traditional' approach mentioned is an 'enhanced' or 'quality by design approach'. The use of one of these terms should be considered instead of 'continuous verification'.** **It is also clear that a QbD approach to development could be taken which does not become a continuous verification approach.** **Proposed change (if any): The use of one of these terms (enhanced or 'Qbd') should be considered instead of 'continuous verification'.**	
Para. 4.4		**Comment: Include matrixing approach with the bracketing approach. Matrixing is similar to bracketing but involves more than two variables. The term matrixing should also be added to the glossary.** **Comment: Include matrixing approach with the bracketing approach. Matrixing is similar to bracketing**	

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		but involves more than two variables. The term matrixing should also be added to the glossary. **Comment: The text now requires that full validation (i.e. at least 3 validation batches) of all marketed strengths for new products. This exclusion of a bracketing/matrixing approach for new products is over restrictive; if there is a sound scientific rational to take a bracketed approach for new products this should be allowable under GMP requirements.** **Proposed change: Revised text "Process validation for new products should normally cover all intended marketed strengths and sites of manufacture. However the number of validation batches could be reduced by the use of a bracketing/matrixing approach (example for different strengths, batch sizes and pack sizes/ container types) where this is scientifically justified.** **Add definition of matrixing to the glossary: "Similar to bracketing, this involves assessment of the effect of multiple variables to identify the worst cases or extreme conditions for that set of variables and using these conditions during validation, instead of including all possible combinations of the variables."**	

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Para 4.7		**Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified. e.g. for a continuous manufacturing process.** **This has to be challenged versus the nature of a product. As an example a sterile product made by aseptic processing does not require such a batch size, where process simulation via MFT is critical.** **Batch size for validation shall be determined by risk analysis with a provision for not being less than 10 or 20% (to be discussed) of the final batch size. Further, continuous manufacture of product should be considered with RTRT measurements taken into account whilst the EMA/CHMP/QWP/811210/2009-Rev1 has been published on March 29, 2012. . This paragraph should be relaxed to accommodate industrial reality.**	
Para 4.12		**Comment: This step requires that the process knowledge for the mathematical models be available. The use of mathematical models may not always be required so there should be some flexibility in this step.**	

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Para 4.13		**4.13 Where validation batches are 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.** **Validation batches benefit of all possible scrutiny and there shall be no restriction for commercial purposes.**	
Para. 4.14, Glossary		**Comment: The definition and restrictions associated with concurrent validation are excessively restrictive and do not take into account the possibility of products or processes that are well understood, or those where revalidation is being performed to manage minor changes.** **Proposed change (if any): Please adopt wording to also allow use of concurrent validation for well understood processes.** **An alternate definition of concurrent validation should be provided that does not restrict its use to only "exceptional circumstances", such as "an approach to validation that permits release of individual batches of product for commercial distribution prior to completion of the validation program."**	

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Para. 4.14, last line		**Comment: The validation approach is defined in each protocol and will depend of each validation study; therefore, if the validation approach is going to be concurrent, should be stated in the validation protocol. The VMP should describe the different validation approaches that are accepted by the manufacturer but cannot be used to identify the approach to be used later for specific projects.** **Proposed change (if any): Change the end of the sentence to validation protocol or VP (if applicable) instead of VMP**	
Para. 4.17		**Comment: "…allow the normal range of variation and trends to be established…" 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): Delete the clause "…allow the normal range of variation and trends to be established…"**	

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Para 4.17 et 4.18		**Clear signals should be given for the 3 batches concept not being acceptable any longer, rather as an indication of what should be acceptable, in particular for products having limited demand, or in the biological area as an example**.	
Para 4.20		**Proposal : Validation protocols should include, but are not be limited to the following:** **a) A short description of the process.** **b) Summary of the CQA's to be investigated** **c) Summary of CPP's and their associated limits.** **10** **~~d) Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion.~~** **~~e~~ d) List of the equipment/facilities to be used (including measuring/** **f) monitoring/recording equipment) together with the calibration status.** **e ~~g~~) List of analytical methods and method validation, as appropriate.** **f ~~h~~) Proposed in-process controls with acceptance criteria and the reason(s) which** **each in-process control is selected.** **g ~~i~~) Additional testing to be carried out, with acceptance criteria.** **~~j~~ h) Sampling plan and the rationale behind it.**	

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		~~k~~ i) Methods for recording and evaluating results. **~~l~~ j) Process for release and certification of batches (if applicable).** **~~m~~ k) Functions and responsibilities.** **~~n~~ l) Proposed timetable.**	
Para 4.20 new		**Comment: Validation report shall also be included under this section on traditional process validation** **Proposed change (if any): "Upon completion of the validation scheme a report documenting the results obtained, duly approved by responsible persons shall be generated and made available for inspection."**	
Para 4.20 e- f		**Editorial: Subsections e) and f) are the same sentence and should be joined to read: "e) List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status."**	
Para 4.20 e		**Comment: Utilities should be included** **Proposed change: Change subsection to read. "e) List of facilities, utilities and equipment to be used….."**	

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Para. 4.21		**Comment: It would be possible to implement PAT-based or RTRT controls without having conducted a QbD approach to development. Please focus section 4.2 on PAT/RTRT not on QbD.** **Proposed change (if any): remove the words "For products developed by a QbD approach" from 4.21.**	
Para. 4.27		**Comment: Use of approved protocol for ongoing process verification is too restrictive – there may be other ways of achieving this, such as using a plan or SOP permits change in criteria as process data is accumulated and process capability is demonstrated over time. The need for quality oversight has already been noted (paragraph 1.3) and does not need repeating here.** **Proposed change (if any): Add as indicated in bold "Ongoing process verification should be conducted *using a protocol, plan or procedure* and a corresponding report should be prepared *periodically* to document the results obtained…"**	
Para 4.28		"…(e.g enhanced sampling) "	

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		Or alternatively reduced sampling.	
Para 4.29		**OPV must be conducted regularly as the previous revalidation (about 3 years)**	
Para 5 (entire section)		**This has to fall under the development part of the applications with extrapolation of results resulting from transportation studies and the stability studies supporting the shelf life. From this set of data time limits wrt temperature exposure has to be determined, including observation of the physical aspects of the products. These studies are necessary in the frame of the EU GDP.** **This section to be withdrawn.**	
Para 5.2		**Comment: In 5.2 it mentions "validation" of transportation** **Proposed change: This should be changed to "qualification" as a transport process is never 100% repeatable due to the many variables involved e.g. weather, vehicles etc.**	
Para. 5.3		**Comment: Studies to select primary packaging materials, performed during product development, and**	

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		shipping studies performed for registration, consider the risks from conditions to which product is likely to be exposed during distribution and marketing over the shelf life of the product. These include humidity, vibration, and handling. These variables should not need to be re-assessed during a product's lifecycle except where required to support changes in packaging materials or shelf life. The routine evaluation of complaints and damages should be used to detect issues that may require changes to product specification (including primary packaging). However, transport delays, failure of loggers etc are transport process failures that do require consideration in a risk assessment. The text should cover the risk-prone elements of the transportation process and not the factors which are covered by the inherent specification of the product and its primary packaging. **Proposed change (if any): Rephrase 5.3 as indicated in bold: A risk assessment should be performed to consider the impact of *variables in the transportation process, other than those conditions which are continuously controlled or monitored, e.g.* delays during transportation, failure of data-loggers, topping up liquid Nitrogen, product susceptibility and any other relevant factors.**	

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Para. 5.4		**Comment: The need to monitor should be risk-based. For example, it could be justified that continuous monitoring of temperature adds no value for a product with no specialstorage conditions, or labeled store below 25/30°C which is delayed at a temperate zone air/seaport or road hub. Registration and ongoing stability studies 'cover' temperature and humidity for the climate zone where product is registered (according to ICH Q1 and QWP guidances). Likewise, continuous monitoring may not be justified for a qualified/validated passive container capable of maintaining required temperature beyond the duration of a delay.** **Proposed change (if any): amend** **5.4: Due to the variable conditions expected during transport e.g. delays at airports, a risk assessment should be performed, considering environmental conditions of the route to <u>which medicinal product sensible to temperature</u> may be subjected, to determine the need for continuous monitoring.**	
Para 6 (entire section)		**This fall under part of the development part of an application. This section to be withdrawn.**	
Para 7.1		**Comment: The current sentence is too general and does not take into account the principle of a risk based**	

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		approach driving the qualification/validation effort. Following risk assessment, utilities (such as plant steam, compressed air for instrumentation), may only require FAT/SAT but no formal qualification (IQ/OQ/PQ). **Proposed change: Add sentence: "When justified by direct product impact or contact or through product risk assessment, the quality of steam, water, air, other inert gases, coolants etc. should be confirmed following installation using the qualification steps described in section 3."**	
Para 8 (entire section)		**This is already part of the new section in EU GMP chapter 6**	
Para 8.2		**This is already part of the new section in EU GMP chapter 6**	
Para 9 (entire section)		**The title reads RE-QUALIFICATION, whereas EU GMP current 5.24 requires "Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results"** **Clarification is necessary between these 2 different**	

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		paragraphs as well why the current provision (when nothing has changed) lifting from revalidation no longer exist in this new section.	
Para. 9.2		**Comment: Visual check alone should be acceptable for minor equipment (equipment that is portable and that can be 100% inspected) for example scoops, lids, etc., if supported by appropriate data and documented justification.** **Proposed change (if any): Recommend to add at the end of the statement "…for this criterion *to be used alone for major equipment (e.g. that for which surfaces cannot be 100% visually inspected). With appropriate data and documented justification, visual inspection is acceptable for minor equipment that can be 100% inspected."***	
Para. 9.3		**Comment: "…and validation with ongoing verification after each batch may be required." For a process where several batches are run consecutively in a manufacturing campaign, it may be justified that cleaning is done at the end of the campaign (prior to product changeover) rather than after each batch of the ongoing campaign. Cleaning after each batch within a production campaign of the same material may be unnecessary and costly.** **Proposed change (if any): Add "…and validation may**	

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		be required with ongoing verification prior to each batch or *product changeover."*	
Para. 9.5		**Comment: Content states cleaning limits "…should be based on toxicological evaluation…" Toxicological parameters are often unavailable and residues limits using this method can be very high. The carryover method (based on Acceptable/Product Daily Exposure, e.g. 1/1000 dose into next product), default limits of 10 ppm and visual detection limits have been practical and achievable methods in use for 20+ yrs. The Tox/PDE method should be considered and included but not as the sole method for establishing cleaning limits.** **Proposed change (if any): amend statement to read "…should be based on toxicological evaluation *or other justified rationale, e.g. Product Daily Exposure,* to determine…**	?
Para. 9.5		**Comment: The use of permitted daily exposure (PDE) as a criterion for cleaning validation is currently being discussed and challenged by Industry in proposed changes to EU Chapters 3 & 5 on shared facilities. Also the documentation of the criteria may not be in the form of a risk assessment but still be equally valid. We also support the approach published last year in a couple of articles on protein degradation and not necessarily having to perform the MAC or a PDE value.**	

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		Please find for your reference the 2 JVT articles that the BioPhorum Operations Group, a biopharma trade consortium has written (http://www.ivtnetwork.com/article/methodology-assessing-product-inactivation-during-cleaning-part-ii-setting-acceptance-limits **Proposed change: Revise section to read: "Limits for the carry-over of product residues should be scientifically justified. The justification limits selected should be documented, including all the supporting references. *If the efficacy of the applied cleaning conditions to degrade and denature the product is demonstrated, then the determination of health based exposure limits using Permitted Daily Exposure (PDE) limits of the active and intact product would not be required. Alternative methods for defining acceptable limits should be justified.* The reduction to safe levels of any cleaning agents used should also be confirmed levels of any cleaning agents used should also be confirmed.**	
Para. 9.10		**Comment: We believe the wording is too restrictive, and does not allow for the use of developing technology (e.g. direct surface analysing methods)** **Proposed change (if any): Change "…or by other means depending on the sampling location" to "…or by other**	

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		***methods if supported by appropriate data and documented justification.*"**	
Para 9.13		**For internal discussion:** Does it mean that so documentary validation for dedicated equipment?	
Para 10 (change control)		NA	
Para 10.2		**Comment: The end of the step states, "Furthermore the possibility of incremental changes should be assessed." The use of the word incremental is not the most appropriate word to use here.** **Proposed change (if any): Suggest replacing "incremental" with "cumulative".**	
Para 10.3		**Comment: For manual processes, this step states that "the continued effectiveness of the process should be confirmed …". If it is a manual process, would this be the effectiveness of the process or for the person doing the cleaning, where there could be variability?** **Proposed change (if any): Please clarify and allow for variations for manual cleaning**	
Para. 11.2		Comment: it is very helpful to have this section reference	

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)*
		management of changes to the starting material in the quality system.	
Para 11.6		**Comment: The wording of this point is not clear and does not add anything that is not covered in other sections (11.1 to 11.5, 11.7) concerning change control.** **Proposed change: Delete section 11.6**	
Glossary(cleaning validation)		**Comment: The definition of cleaning validation does not seem optimal. It states to remove <u>all traces</u> of the previous product used in the equipment. This is limited by the technology to test for trace levels. How would you prove that you have removed all traces? Should also refer to general contaminants (cleaning agents) and not just product.** **Proposed change (if any): Please change to read, "…that an approved cleaning procedure will bring the level of previous product and contaminants below the scientifically set maximum allowable carryover level."**	