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Reference: QAS/16.673: GUIDELINES ON VALIDATION - APPENDIX 6: VALIDATION ON QUALIFICATION OF SYSTEMS, UTILITIES AND EQUIPMENT

Dear Dr. Kopp,

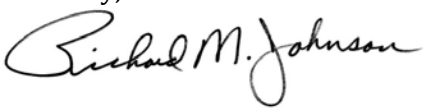
PDA appreciates the opportunity to comment on this draft guideline and commends the WHO for continuing to emphasize harmonization of global requirements. In this draft, PDA notes where terms could potentially be used and defined more consistently with international standards such as: quality risk assessments (versus impact assessments).

For clarity, PDA recommends the inclusion of examples of ICH practices that will further the efforts to harmonize guidelines worldwide. For example, quality risk management may be embedded in qualification activities, determining the scope and frequency of calibrations, and qualification of "in use" equipment. To minimize potential harm to product and patient safety, the extent and scope of qualifying "in use" equipment should be based on risk.

PDA also notes that use of the term "all" within the document can be interpreted as fully inclusive, which may not be the intention for every instance. PDA also recommends reconsideration of using example/forms, as they too may be prescriptive for those referencing this guidance for their validation practices. We have provided specific examples within the comment matrix for each.

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 and biological manufacturing including members representing the Science Advisory Board, Process Validation Task Force, Quality System subject matter experts, and the PDA Board of Directors.

If there are any questions, please do not hesitate to contact me.
Sincerely,



Richard Johnson
President and CEO, PDA

Cc: Jahanvi Miller, PDA; Richard Levy, PDA

Comments on WHO Working Document QAS/16.673
Title of the document: Guidelines on Validation - Appendix 6: Validation on Qualification of Systems, Utilities and Equipment

Comments submitted by : Parenteral Drug Association
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Date : 23 AUG 2016

*Kindly complete the table **without modifying the format** of the document - thank you.*

Template for comments

General comment(s) if any :	**Originator of the comments**
PDA recognizes that there are standard terms and language already in existence that encompass risk-based approaches and techniques, which may provide added clarity to certain aspects of this guidance. We recommend efforts be made to align with these existing standards (ICH Q9 guidance).	
Critical Comment (s): Quality risk management can be embedded in qualification activities (line 181), determining the scope and frequency of calibrations (line 335), and qualification of “in use” equipment (452). To minimize potential harm to product and patient safety, the extent and scope of qualifying “in use” equipment should be based on risk. The use of terms, “all” needs to be clarified as the meaning of that terms can be interpreted to be all inclusive. There are some uses of the term “all” which do not necessarily apply where used (comments below indicate exact context in the document). PDA would recommend “all” be removed in those instances if specific examples are not provided. Periodic review is an important element even where requalification is deemed not to be necessary. PDA recommends that consideration be given to include this element within section 11 on requalification. We recommend that consideration be given for removal of the forms from within this document. PDA considers the template/example forms may be too prescriptive and may not encompass all elements of the systems, utilities, and equipment. There is great potential for misinterpretation of these forms and their intended use. They also may have the potential to be contradictory to the quality management system processes; refer to cGMP deviation quality management system.	

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
2.3	179	Consider what is being qualified, in this instance we are not qualifying the quality control of a system; or is that what is meant? Clarification is needed on what is meant in this instance (is it a QC laboratory or QC of equipment).	Perhaps remove "quality control of" and replace with "laboratory equipment". …steam systems; production and ~~quality control of~~ **laboratory** equipment and instruments.	H	
2.4	181	Some rewording can potentially improve clarity and adding alignment with existing ICH Q9 guidance can improve efforts towards harmonization.	Consider replacing impact with quality risk, and revise to …. "Documented quality risk assessment should support decisions for qualification testing." Documented ~~impact~~ **quality risk** assessments should support decisions for ~~the exclusion of systems, utilities and equipment from~~ qualification **testing**.	M	
3	203	Utilities are missing from the equipment and systems list (scope alignment), also it is important to clearly define what exactly is being reproduced. It is unclear what can be considered as a prolonged period, if it is not defined or ranges are not provided.	**Performance qualification**. Documented verification that the equipment, system, or **utility** operates consistently and **yields reproducible results** within defined specifications and parameters. ~~for prolonged periods. (In the context of systems, the term "process validation" may also be used.)~~ Or use modified version of section 10.1 definition: **Systems, utilities, and equipment which consistently perform in accordance with their design specifications; the performance should be verified in accordance with a PQ protocol.**	H	
4.2	227	Minor adjustments would increase harmonization with ICH terminology.	Replace "impact assessment and risk assessment" with "quality risk assessment". **Quality** risk management principles should be considered in ~~all areas of~~ the scope ~~stages~~ **and extent**	M	

			of qualification **and requalification.**		
4.3	235	PDI and UAT in the figure are not defined. Please define/ spell out acronyms or remove from figure.	Footnote or add in text what the PDI and UAT acronyms are, as done for FAT, DQ etc. The diagram is potentially outdated and could be improved by applying a risk-based approach across multiple jurisdictions. As is, it implies that all elements of the URS and design specifications must be tested in qualification. If this document is to follow the V-model, then approval of the DQ test report is a pre-requisite for the start of the build phase of the system lifecycle (Line 322 needs to be updated also).	H	
4.10	260	Line 260 is unclear; room and area qualifications are dependent upon the utilities. Utilities should be qualified prior to the qualification of equipment. Also renumber sections that follow as needed if this section is removed.	Delete line 260 and revise 262 to read, "Utilities should be qualified prior to the qualification of rooms/areas and equipment." ~~4.10 Rooms or areas, as appropriate, should be qualified prior to the qualification of utilities.~~ 4.1**0**~~1~~ Utilities should be qualified prior to the qualification of **rooms/areas and** equipment.	H	
4.12	264	The term "be" is missing from this statement.	Equipment should **be** qualified…	L	
4.16	279	Periodic review is an important element as well, and in some instances may be sufficient instead of periodic requalification.	Systems, utilities and equipment should be maintained in a qualified state and undergo periodic **review and/or** requalification **as** appropriate, as well as requalification after change, when needed.	M	
4.17	282	Test methods should also be validated on qualified equipment.	Processes **and test methods** should be validated on qualified equipment.	M	
5.2	289	Clarification needed to define the intended party.	Change manufactures needs to user needs; URS is generally intended for users. utility or equipment is in accordance with the ~~manufacturer~~ **user**'s needs as specified.	H	
6.1	294	Increased alignment with ICH (referred to in cover	add "based on QRM principles";	M	

		letter).	than that of the purchaser or end-user, testing and verification **based on QRM principles** ~~should be done to~~ ensure**s** that the		
8.4	335	"Calibration" needs clarification as to which party is responsible or whether vendor documentation can be used.	~~Measuring, control and indicating devices being installed should be calibrated~~ **Calibration requirements need to be based on risk assessment, including use of vendor supplied documentation, or if on-site calibration is required.**"	L	
8.7	348	Follow-up action should be mentioned (i.e. CAPA) for consistency and alignment with ICH.	Replace with: should be recorded, investigated, addressed and/or corrected. observed during installation, should be recorded, ~~and~~ investigated, **addressed and/corrected.**	M	
8.8	350	"The outcome of the IQ should be recorded in the conclusion of the report, before OQ is started." It is generally accepted that for some more simplified equipment and systems that IQ is combined with OQ. See EU Vol. 4 on GMPs, Annex 15 and PIC/S GMP Guidelines (Annex 15) on Qualification and Validation (2015), item 3.10., add a statement to reflect as such.	Revise to read as follows: **Depending on the simplicity of the equipment or system, the IQ may be combined with the OQ.**	M	
8.9	354	"During" may not be the appropriate time; may be restrictive.	Add "before", infront of OQ. up ~~during installation.~~ **before OQ.**	M	
8.9	357	Figure 2/ Example of IQ protocol Deviations should be covered by deviation quality system. The form in the document does not mention investigation, or CAPA. The forms may be too prescriptive and can't encompass all elements of the systems, utilities and equipment. They have the potential to be misinterpreted and potential to be contradictory to the quality management system (referred to in critical comments).	Remove example. Remove deviation form; instead refer to cGMP deviation quality management system. Remove all format for an Installation Qualification Protocol and Report form examples.	H	
9.3	373	This may not be true always as implied here; Also clarification is needed on if there is a room for using QRM or risk based concept to determine the OQ testing required vs. asking for all system elements	Remove "all" from system elements OQ should include verification of operation of ~~all~~ system elements, parts, services,	M	

		verification (referred to in critical comments).			
9.9	395	Figure 3/ Example of OQ protocol: Remove deviation form; instead refer to cGMP deviation quality management system. Deviations should be covered by deviation quality system; form in the document does not mention investigation or CAPA. CHART 6: Per 9.2 on OQ, critical operating parameters should be identified. However, there is no section of the Protocol Example on pages 17-26 where critical operating parameters are listed. There is Chart 6 on pg. 24 for challenges, but nothing specified for critical operating parameters (referred to in critical comments).	Remove example as companies may end up following blindly even if it may not applicable in all instances.	H	
10.2	414	Figure 4/ Example: On line 414 (and figure) it states "Manufacturers should justify the selected period over which PQ is done" yet the protocol example on page 30 has no provision for this justification. It simply states "Run for 20 consecutive working days…" The example protocol should have a section for that justification or explanation of why the 20 days is sufficient (referred to in critical comments).	Remove example, if forms are not deleted then add section for justification of selected period of PQ, around page 30 of the protocol. There should also be a section in the protocol to justify the selection of the 3 times. ("Run normal procedure 3 times…).	H	
11.	437	Periodic review is an important element even where requalification is deemed not to be necessary. The guideline could add this concept to this section.	Update section title to "Periodic Review and Requalification".	M	
11.2	442	Periodic review is an important element even where requalification is deemed not to be necessary. The guideline could add this concept to this section. Routine requalification of systems, utilities and equipment should be considered based on the outcome of risk management principles which include factors such as calibration, verification and maintenance data and information.	Revise to "Periodic review and/or requalification of systems, utilities, and equipment should be performed based on an assessment of risks, which **may** include factors such as calibration, verification and maintenance data, and information.	M	
11.3	446	Periodic review is an important element even where requalification is deemed not to be necessary. The guideline could add this concept to section 11.3. The	The qualification status, **periodic review and/or** requalification due dates should be documented in a defined schedule.	M	

		qualification status and requalification due dates should be documented in a defined schedule.			
12.	452	For qualification of already “in use” equipment, one must conduct a risk and impact assessment on the prior production exercise to determine the impact of not doing IQ/OQ prior to writing any protocols (referred to in cover letter).	Add guidance for already “in use” equipment to "conduct quality risk assessment on the prior production exercise to determine impact of not doing IQ/OQ prior to writing any protocols."	M	