Parenteral Drug Association

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1946 70TH ANNIVERSARY 2016

Bethesda Towers
4350 East West Highway, Ste 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

August 22, 2016

Dr. S. Kopp
Medicines Quality Assurance Programme
World Health Organization
1211 Geneva 27, Switzerland
kopps@who.int

Reference: QAS/16.671 Guidelines on Validation: Appendix 4 Analytical Method Validation

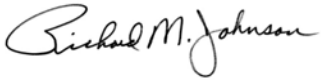
Dear Dr. Kopp,

PDA appreciates the opportunity to comment on another validation related draft guideline. PDA notes some of the terminology used in the document is not clear or wording is undefined and seems inconsistent with other global standards. PDA recommends checking for consistency with other related WHO standards and adding a glossary of terms to include references. In addition PDA suggests adding a reference to ICH Q2 (R1) Validation of Analytical Procedures at the beginning of the document in order to clarify that the underlying principles described in the WHO guidance are based on the related ICH document. PDA also recommends clarification that stability indicating is not the only criteria to determine when to validate an analytical method and that validation can be performed by different functional groups at different companies.

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, the Regulatory Affairs and Quality Advisory Board, and Board of Directors.

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

Sincerely,



Richard Johnson
President and CEO, PDA

Cc: Ms. Marie Gaspard, WHO; Denyse Baker, PDA; Richard Levy, PDA

Comments on WHO Working Document QAS/16.671

Title of the document: GUIDELINES ON VALIDATION – APPENDIX 4 3 ANALYTICAL METHOD VALIDATION 4 (June 2016)

Comments submitted by : Parenteral Drug Association
Telephone number : 301-656-5900
Address : 4350 E. West Highway Suite 600 Bethesda, MD 20814
Email : Johnson@pda.org
Date : August 22, 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**
Some of the terminology used in the document is not clear or wording is undefined and seems inconsistent with other global standards. PDA recommends checking for consistency with other related WHO standards and adding a glossary of terms to include references.	

# section	**Line no.**	**Comment / Rationale**	**Proposed change / suggested text**	**Classification** L= low M= medium H= high	**Originator of the comments (for WHO use)**
	149	Recommend to provide reference to ICH Q2 (R1) *Validation of Analytical Procedures* at the beginning of the document in order to clarify that the underlying principles described in the WHO guidance are based on the related ICH document.	1.1 This appendix presents some information on the characteristics that should be considered during validation of analytical methods **that are based on the general principles laid down in ICH Q2 (R1) Validation of Analytical Procedures.**	L	
	157	Validation is required for those methods used for quality control purposes. Stability indicating is not the only criteria for when to validate a method.	Analytical methods, **used in quality control purposes for commercial release and stability** ~~whether or not they indicate stability,~~ should be validated.	H	

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	159	Validation could be performed by different groups in different companies.	**The analytical method used for commercial product lot release should be consistent with the validated analytical method.** The analytical method should be validated ~~by research and development~~ before being transferred to the quality control unit when appropriate.	H	
	162-163	Recommend deleting this statement. It isn't clear to which recommendations this is referring. There is no GLP reference as part of the guideline. Tech Transfer is a wider operation in which analytical method validation is only one part.	~~The recommendations as provided for in good laboratory practices and guidelines for transfer of technology should be considered, where applicable, when analytical method validation is organized and planned~~	L	
	168	Recommending more specific wording than "materials"	There should be specifications for ~~both materials~~ **drug substance, excipients** and drug products. The tests to be performed should be described in the documentation on standard test methods.	L	
	171-172	Validation occurs prior to approval so this language is unclear. PDA recommends using the terms "acceptance criteria" and "test methods" which together make a specification.	~~Specifications~~ **Acceptance Criteria,** and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed **and validated** ~~specifications or~~ test methods **and related acceptance criteria** ("non-pharmacopoeial methods") ~~as approved by the national regulatory authority (NRA)~~ may be used.	L	
	178-179	Recommend removing the entire 2.4. A quantitative test is the same as a limit test. Recommend aligning with ICH Q2R1 Test categories. The examples given are not comprehensive.	~~The most common analytical procedures include identification tests, asssay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.~~	L	
	184	In some cases there are legal requirements for retention of data beyond what a laboratory may define.	All results should be archived ~~for an appropriate period oftime as defined by the laboratory and be~~ in compliance with National Regulatory Authority (NRA) **and any other legal or Regulatory requirements.**	L	
	193-199	For clarity, remove reference material description as any of these changes are covered by change control as	2.8 Changes to methods should be managed in accordance with the authorized change control	L	

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		described in the first and last sentences.	procedure. ~~The variability of reference materials and other factors such as… or when major pieces of equipment instruments change should be considered. These should be understood, controlled and, where possible, reduced.~~ Verification or revalidation should be considered where appropriate.		
	204-205	More clarity on training needs	… analysts, who are responsible for ~~certain~~ **validated** tests, …..	L	
	208	Better readability	… should ~~be considered covered~~ **comply with** ~~by~~ good anything practices requirements (GxP) and …	L	
	233	More clarity	…under consideration ~~(~~no ~~placebo~~ interference **from other constituents of the drug product**~~)~~.	L	
	242	Clarify the validation criteria.	Validation should be performed in accordance with a validation protocol. The protocol should include procedures and acceptance criteria for all **required validation** characteristics.	L	
	249	Delete “standard”, not needed	~~Standard~~ Test methods should be described …	L	
	251/252	It is recommended to avoid a focus on specific analytical methods (here: chromatography), but provide general advice.	As a minimum, the description should include the ~~chromatographic~~ **analytical** conditions ~~(in the case of chromatographic tests),~~	L	
	257	Add clarity	Method verification ~~consists of~~ **requires** partial validation. Verification should be performed ~~for already validated analytical methods~~ under the following circumstances:	L	
	269	Delete after last comma, too specific for one type of method	… all potential impurities~~, even the late eluting ones~~. Specificity …	L	
	269-270	Change word for consistency in use of terms	Specificity should be among the **characteristics** ~~tests~~ considered (see sections 9 and 10 below for more detail).	L	
	275	Recommended to use ‘common’ wording.	Methods should be maintaned in a validated state over the life**cycle** of the method ...	L	
	276-277	Change this wording so that this is an example, otherwise , too specific for one type of method	Revalidation of an analytical procedure should be considered whenever there are changes made to the	L	

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			analytical method ~~including:.~~ **For chromatography methods these include:**		
	285-287	Better readability and clarification of what leads to revalidation.	In case of repeated system suitability failures ~~or when obtaining of doubtful results~~ ~~In such cases~~ an investigation of the root cause should be performed. ~~, the appropriate changes made and the method revalidated, if necessary.~~**If this leads to changes in the method, revalidation should be considered.**		
	292 / 293	Recommend to use unequivocal wording	8. **Analytical** Method Transfer 8.1 During **analytical** method transfer, documented ...	L	
	293	Recommend to provide a definition of 'Analytical Method Transfer' (according to PDA's TR N° 57 or 65) by adding a new section at the start of part 8.	**New section 8.1: In general, (pharmaceutical) technology transfer consists of planned and controlled actions that are based on well-defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as sending unit (SU), to a new site, the receiving unit (RU) (Reference PDA TR N° 57 or 65).**	L	
	294	Recommend to use unequivocal wording and provide a definition that has already been commonly used (e.g. from ISPE Technology Transfer Guide, 2003 and PDA TR N 65).	8.1 During **analytical** method transfer, documented evidence should be established to prove that a method **can be reproduced against a pre-defined set of specifications** ~~has equivalent performance~~ when used in a laboratory different from that where it has been originally validated.	L	
	303	Recommend to use 'pre-determine' because it is important that these criteria be established in advance.	8.3 The two sets of results should be ~~statistically~~ compared and the differences between the two sets of tests should be within a~~n~~ **pre-determined** acceptance ~~range~~ **criteria**.	M	
	305-306	Recommend to use unequivocal wording to clarify that only the receiving laboratory requires assay transfer before testing can occur. 'Critical data' during method	8.4 Method transfer should be performed before **the receiving laboratory conducts** testing of samples for obtaining critical data ~~for a dossier~~, such as process	H	

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		transfer are not obtained "for a (submission) dossier", but form part of the transfer and will be documented in the related transfer protocols.	validation or stability studies or ~~applied for~~ in routine ~~use~~ **manufacturing**.		
	308	Recommend to use unequivocal wording. It is important for both the sending and receiving units to agree on the protocol.	8.5 A predefined **and mutually signed transfer** protocol should be followed which includes at least ...	M	
	315	"independent testing entity" is misleading – could also be an "independent contract laboratory". Recommend to use unequivocal wording	8.6 In the case of **testing by an independent** ~~testing by a separate entity an official~~ **laboratory**, such as a national quality control testing ...	L	
	321-334	Recommend to use unequivocal wording (see also comment to line 417); recommend to define the validation characteristics in an attached 'Glossary' instead of listing them as part of the core document (see ICH Q2 R1).	9. **Validation** Characteristics of Analytical Procedures ~~9.1~~ **Typical c**~~C~~haracteristics that should be considered during validation of analytical methods include: (...) **Each of these validation criteria is defined in the attached glossary.** ~~This list should be considered typical but occasional~~ **E**~~e~~xceptions should be dealt with on a case-by-case basis.	L	
	322ff	Recommend to provide the definitions of the validation criteria either in the same order as these are listed in chapter 9.1 'characteristics' – or alphabetically.	**Glossary** <recommend to include chapters 9.11 to 9.1.8 into the 'Glossary>.	M	
	328	Recommend to match list of 'characteristics' (chapter 9.1) with definitions as provide in chapter 9.1.1.ff in order to avoid confusion	- Precision o **Repeatability** o **Intermediate precision**	L	
	339	Recommend to reference ICH Q2-R1	Accuracy should be established across the specified range of the analytical procedure **(ICH Q2 R1).**	L	
	346/347	Recommend to use commonly use 'technical terms'	It should be measured by the scatter of individual results from the **arithmetic** mean ~~(good grouping)~~ and expressed as the relative standard deviation (RSD).	L	
	353-355	Intermediate precision is required; it is independent of reproducibility (inter-laboratory)	Remove: ~~If reproducibility is assessed, a measure of intermediate precision is not required.~~	L	

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	408-416	Add an additional bullet to match the ICH guidance reference listed in Section 7.	Add one additional bullet to the list: - **Recommended Data**	L	
	417-418	Recommend to use unequivocal wording (see also comment to lines 321-334); “including tests” is misleading – recommend to delete this. Recommend to use a wording in harmony with ICH Q2-R1 in order to avoid misunderstanding (table lists most important validation criteria).	9.2 **Validation** characteristics ~~(including tests)~~ **that** ~~should be considered~~ **are regarded as the most important for the validation of** ~~when using~~ different types of analytical procedures are summarized in Table 1.	L	
	425-426	Recommend to use usual unequivocal ‘technical terms’	An appropriate number of samples ~~to provide adequate statistical power and ranges~~ should be considered.	L	