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September 20, 2019

World Health Organization
Medicines Quality Assurance
kopps@who.int
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Reference: Production of Water For Injection By Means Other Than Distillation (February 2019) Draft Guidance

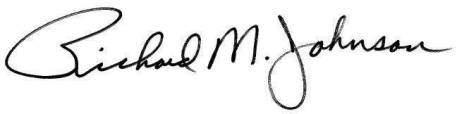
Dear World Health Organization:

PDA appreciates the opportunity to respond to World Health Organization Consultation on: Production of Water For Injection By Means Other Than Distillation. PDA fully supports the WHO's PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION (July 2019) Draft Guidance, as it advocates a risk-based lifecycle approach. The WHO Draft Guidance deems to incorporate latest changes in European Pharmacopeia and other global regulatory and standards guidances. PDA supports flexible approaches for products currently manufactured to avoid interruption of supply of essential medicines. PDA is also working to harmonize language across guidances as a global effort to increase the implementation of standard processes. Therefore, PDA has no additional comments for draft guidance with exception of the following proposed revisions of minor inconsistencies for considerations of authors as listed in the comment form.

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 pharmacopeia publications including members representing our Board of Directors and our Science Advisory Board.

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

Sincerely,



Richard Johnson
President, PDA
Cc: Tina Morris, Janie Miller

Comments and suggestions from reviewer

Title: WHO's PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION (July 2019)

DRAFT FOR COMMENTS

Reviewer (name, position, full contact details):

Comments submitted by : Parenteral Drug Association (PDA)
Telephone number : 001-301-656-5900
Address : 4350 East West Highway, Bethesda MD, 20854 (USA)
Email : miller@pda.org
Date : 20September2019

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General/Overall comment				
	PDA fully supports the WHO's PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION (July 2019*) Draft for Comments Guidance*, as it advocates a risk-based lifecycle approach. The WHO Draft Guidance incorporates latest changes in International and European Pharmacopeia, as well as other global regulatory and standards guidances. PDA advocates flexible approaches for products currently manufactured to avoid interruption of supply of essential medicines. Therefore, PDA has no additional comments for draft guidance with exception of the following proposed revisions of minor inconsistencies for considerations of authors.			
Title: PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION Working document QAS/19.786 (July 2019)				
2. SCOPE				
105-107	2.1 This document provides guidance for the production of WFI by means other than distillation. The principles described in this guideline may	The lifecycle approach, the risk management practices, specified controls and other requirements and technical recommendations should not	2.1 This document provides guidance for the production of WFI by means other than distillation. The principles described in this guideline may	

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	be applied to other grades of water produced, meeting other specifications.	be specific to WFI generation method, these represent good practice for all WFI systems including distillation systems.	be applied to other grades of water, as well as WFI produced by other methods (including distillation), meeting other specifications.	
5. RISK ASSESSMENT				
141-143	5.3 Risks identified should be assessed to determine the scope and extent of validation and qualification of the system, including the computerized system, used for the production, control and monitoring of WFI.	Recommend adhering to ICH Q9 Quality Risk Management.	5.3 Risks identified should be analyzed and evaluated to determine the scope and extent of validation and qualification of the system, including the computerized controls, used for the production, control and monitoring of WFI. Risk management should be an ongoing part of the quality management process for WFI. A mechanism to review or monitor events associated with production, storage, distribution and use of WFI should be implemented.	
154	controls are in place to prevent dead legs and contamination;	Remove redundancy as “contamination” already stated in line 148 (assuming it is all inclusive sources of contamination).	controls are in place to prevent dead legs;	
6. CONTROL STRATEGY				
173-175	6.6 Techniques such as deionisation, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be	It should be noted that ozonation can be an effective system treatment and there can be advantages to storing water (at ambient temperature) with an ozone residual.	6.6 Techniques such as deionisation, ultrafiltration, water softening, descaling, pre-filtration and degasification, ozonation, ultraviolet treatment, along with other techniques,	

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	considered in conjunction with a double pass reverse osmosis (RO) system).		may be considered in conjunction with a single-pass or double pass reverse osmosis (RO) system).	
7. GOOD PRACTICES IN THE PRODUCTION OF WFI				
200-203	7.3 Where RO is used, single or double-pass RO, coupled with other appropriate techniques such as electro-deionisation (EDI), ultrafiltration (UF) or nanofiltration, should be considered. The purification process employed should be proven to be at least equivalent to distillation.	First sentence is inconsistent with Section 6.6 (Line 175). Second statement is aspirational. Firms that do not have distillation experience in the same setting and with the same feed water may find this impossible to demonstrate.	7.3 Where RO is used, a single-pass or a double-pass RO, coupled with other appropriate techniques such as electro-deionisation (EDI), ultrafiltration (UF) or nanofiltration, should be considered. The purification process must be proven to reliably meet the compendial requirements for water for injection.	
211-213	Appropriate action and alert limits in addition to specification limits should be specified. Alert and action limits should be reassessed routinely to enable, where possible, a re-evaluation of those control limits.	Use the trend data (see section 7.5) for evaluation of the limits instead of the alert limits. It is common practice in the pharmaceutical industry to calculate process capability on a statistical basis to evaluate suitable alert levels (example in ICH Q8(R2), Appendix 1). Therefore, the trend data is used.	Appropriate action and alert limits should be specified. Trend data should be reassessed routinely to enable, where possible, a re-evaluation of those control limits.	
215-217	The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, pH, total organic carbon (TOC) and microbial contamination.	Water with low conductivity contains no more buffer for pH testing. Therefore, measuring pH in water for injection does not bring additional information for the user. The pH is not a valuable measurement in WFI.	The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, temperature, total organic carbon (TOC) and microbial contamination.	

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219-221	A combination of online and offline monitoring of WFI should be done to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with on-line instruments.	Inline testing provides better process control. The parameters conductivity, TOC and microbiology can be tested inline (conductivity) resp. online (TOC, microbiology, refer to the new Ph. Eur. 5.25 draft). For TOC and conductivity, online measurement can be used for releasing water for pharmaceutical purposes. The currently existing microbial rapid methods for water testing provide additional process control but may not be used for quality control yet (Major firms performed or are currently performing studies). As such, offline microbial testing is the only possibility for QC purposes, at a time. For TOC and conductivity, offline testing could only be used as a backup process in the case of problems with online sensors. Propose to include rapid micro technology, as it is currently being installed.	A combination of online and offline monitoring of WFI should be done to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with on-line instruments. If possible, in-line or online technology shall be used to control the water system and to release the water for pharmaceutical use. Use of rapid microbiological methods is encouraged for timely monitoring and aid with rapid responses to prevent deterioration of the system.	
REFERENCES				
3	Add ICH Q9 Quality Risk Management Guidance	As Risk Management is introduced, a global guidance should be added to References	ICH Q9 Quality Risk Management Guidance	
3.	Add ISPE Handbook:	Add the new ISPE Handbook for	ISPE Handbook: Generation of	

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	Generation of water for injections without distillation	WFI to your references. German version already available here: https://ispe-dach.org/die-ispe-dach-arbeitsgruppen/regional-cop-pharma-wasser-und-dampf/; we will provide information about the English version in the next months when available.	water for injections without distillation	