Comments on WHO Working Document QAS/19.786
Title of the document: PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION

World Health Organization

Comments submitted by: International Society for Pharmaceutical Engineering (ISPE)
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Date: 13 April 2019

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

General comment(s) if any:	**Originator of the comments**
The document is very high level and would be improved by adding more specific guidance. In several places the documents states that there should be "no risk" but there are few engineering options that meet a no risk requirement – detailed suggestions are provided below.	ISPE

# section	Line no.	Comment / Rationale	Proposed change / suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
1.2	58/59	Redundant text.	Suggest deleting "Water or required quality for its intended use should be produced by appropriate methods."	M	
2.1	64/65	Statement is unclear.	The principles described in this guide may be applied to water systems providing water meeting other specifications.	H	
2.2	67/68	Consider deleting this section as it is not relevant to the scope of this document	Consider adding references to other useful documents, e.g. the ISPE Guidance documents.	M	
3	72-79	Recommend defining the requirements in this section.	The manufacturer must have an internal specification for WFI.	H	

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			WFI must meet the Pharmacopeial monograph that apply to the markets the facility will supply. Where the manufacturer supplies multiple markets with different Pharmacopeial monographs, the principle of using the most onerous requirement may be applied to develop the company internal specification		
4	83-91	Recommend covering the system lifecycle in this section.	The design of a WFI system should define the pre-treatment and treatment stages, and consider the impact of failure of these stages on the WFI Quality The operational procedures should ensure the pre-treatment and treatment stages are appropriately monitored The maintenance procedures should describe the necessary maintenance (activities and frequencies) for each stage and define component lives Decommissioning of the system should follow a defined process, with close out calibration of all critical instruments The manufacturers quality system must define the actions required in the event of a failure of the WFI to meet the specifications.	M	
5.1	95	Recommend providing additional guidance.	An appropriate Risk Assessment method should be used considering ICH Q9.	M	
5.3	100/102	Recommend revision to expand on 5.2.	Risk controls defined in the risk assessment should be verified through the commissioning and qualification process and continuous verification process	M	
5.4	104/114	The paper is for non-distillation processes; text could be more concise, and a no risk scenario is not practical.	System user requirements should be developed. The likely variation in system feedwater quality should be defined. The pre-treatment and treatment stages should be	M	

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			defined by a specialist supplier / subject matter expert considering potential variation in the feedwater quality. There must be sample points between each process stage. The design should consider use of instrumentation to monitor each process stage for parameters that could impact the WFI quality.		
6.1	118	A no risk scenario is not feasible.	Consider deleting 6.1 or revise to there should be minimal risk of contamination.	M	
6	120/153	Suggest providing guidance in a more structured way. Line 138: Suggest organic is too limiting a description; Line 141: Please consider why electrolytical scale reduction - which is a trademark of Biopuremax, patented to Shlomo Sackstein - is singled out; Suggest degasification between RO stages would cause operational issues.	The minimum standard for feed to the system is potable water. Feedwater quality should be monitored System design should minimize risk of degradation of the water quality, considering water should not be stagnant, deadlegs should be minimized (including in the pre-treatment plant), temperature should be controlled to ensure consistent system operation. Any connection to a drain should have an air break of at least 30 mm Equipment should be selected such that it is sanitized through its operation or is capable of being sanitized, e.g. providing a chlorinated feed to a softener – with the benefit of maintaining microbial control accepting a reduced resin life compared to using the softener with a dechlorinated feed. There should be a validated sanitization process for the pre-treatment and treatment plant Materials of construction must be fit for the intended use ie not be reactive, additive or absorptive to adversely affect the quality of water produced– e.g.	H	

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			uPVC, PVDF, SS 316/316L Construction and inspection standards should be defined Gaskets should be food grade and have a defined life (there are references that could be added here from USP) Water velocity should be such that turbulent flow exists (Re number greater than 3000) Sample valves should be provided between process stages – the specification should consider the characteristic being sampled for, i.e. sanitary valves should be used where microbial testing will be conducted. The storage and distribution system should be capable of being routinely sanitized, with the sanitization regime validated. Systems operating at over 70 degrees C are considered self-sanitizing Points of use should drain, and connections to equipment should drain. Any flexible hoses should be removed and hung so that they free drain when not in use.		
7.1	157/158	Covered in the suggested content for 6.	Recommend deleting.	M	
7.2	160/161	Given the title of the guide it seems inappropriate to state that distillation is preferred.	Suggest deleting or replacing with “Distillation has been the industry standard for production of WFI. Newer and different technologies and production modules used in non-distilled WFI can produce WFI quality water with equivalent or better quality than distillation.”	M	
7.3	163/166	Suggest revising the text to provide clarity.	When RO is used with other modules to produce WFI, selection of process modules may include one or	M	

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			many process modules of ion exchange, electrodeionization (EDI), dual pass RO, ultrafiltration, ozone, microfiltration, nanofiltration, and UV. Selection should be based on the purification steps needed to produce WFI meeting the compendial requirements that can be validated.		
7.4/7.5	168/169	The statement repeats section 3. Suggest revising to an action statement with more specific guidance.	The system should be routinely monitored using on line continuous monitoring where practical, and a supporting rationale for the test and schedule, including the pre-treatment, treatment, storage and distribution system. Test results should be trended on an ongoing basis with a review report produced every quarter	M	
7.7	176	This statement does not provide guidance.	Suggest deleting the section as it repeats earlier statements or replace with "There should be minimal risk."	M	
7.8	179	This statement should be rewritten to provide guidance.	The system should be validated and remain in a validated state through the following systems: • Maintenance and calibration • Change management • Non-conformance CAPA • The as built record drawing should be verified periodically	M	
7.9	181/183	We suggest that it is not considered necessary to monitor pH unless the system has performance issues.	Recommend deleting section.	M	
7.10	185	We believe that this statement to be incorrect: "Inline sampling and testing should be supported by off-line testing." In this case the expectation would be for every site to have both on-line testing and off-line testing for every parameter. I-line testing can be used for product	Samples should be taken from points of use (including any hoses routinely used) to confirm compliance with the specifications for TOC, microbial and endotoxin (Conductivity is not considered necessary as there is very low risk of the use point influencing this	M	

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		release without off-line testing confirmation. It is costly and unneeded to have both.	parameter)		
7.11	187	Recommend rewriting this statement to provide guidance as to how to monitor,	Where RO systems are used the feed and discharge quality should be routinely monitored for endotoxin to ensure the system is operating to meet the specifications.	M	