Comments on WHO working document QAS/19.786/Rev.1
TITLE OF THE DOCUMENT: **PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION**

World Health Organization

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Date: 13 August 2019
*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**
The document would be improved by the inclusion of more practical guidance and examples that a potential user would find helpful. An overview of the technologies and pros and cons would be a helpful addition.	

# section	Line no.	Comment/Rationale	Proposed change/suggested text	Classification **L**= low **M**= medium **H**= high	Originator of the comments (for WHO use)
	55	It would be good to align the language here with that used in the pharmacopeia, to allow some flexibility in the chosen solution.	Suggest replacing 'equivalent to' with 'minimally', 'at least equivalent', or 'superior to'. "The monograph revisions in a number of pharmacopoeias were the result of extensive consultations with stakeholders and now allow production of WFI by a purification process ~~equivalent to~~ **minimally or at least** equivalent **or superior** to distillation – such as reverse osmosis – coupled with appropriate techniques".	L	

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1	100	Since the text provides very little information it dilutes the value of the document.	Suggest deletion: "~~Water of required quality for its intended use should be produced by appropriate methods~~".	M	
3	120	Consider revising the sentence to provide clarity.	"WFI should meet the ~~specification~~ **requirements defined by the** ~~as published in current monographs of the~~ Pharmacopoeia~~, recognized by the Medicines Regulatory Authority~~ **of the country the product will be supplied to"**.	M	
4.0	125	As written the text does not provide guidance. We suggest rewriting it so that it provides practical guidance, retitled as monitoring strategy. Add a section on "lifecycle" requiring the operating limits to be defined for the system components, so that an appropriate maintenance and replacement program can be defined. Process steps in the pre-treatment should be defined as well as their function. Risk based approaches should be used to define the relevant failure modes of each step, and an appropriate monitoring and control strategy implemented.	Proposed Language: "**1) A softener is used to remove salts from RO feedwater that would build up on the membrane reducing capacity. In the event of failure, output would be reduced, and cleaning required – these are considered business risks; to address this risk, a good engineering practice of routine testing of the feedwater hardness will be implemented.** **2) The RO system is used to remove contaminants, endotoxin and microbial contamination from the feedwater. Failure / degradation of the membrane, or an O ring could result in water exceeding the specifications that can be treated by subsequent stages. These failures (degradation of the membrane or O ring failure) would be detected by a change in the RO output conductivity – this is therefore a critical parameter that should be monitored and alarmed**".	M	

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5.1	137	We propose that the existing text can be deleted– note that section 4.0 provides a practical example of applied risk management for the expected reader	Suggest deleting: "~~An appropriate method for the production of WFI should be used~~".	M	
5.3	141	The text should provide practical guidance on defining expectations.	Suggest replacing the current text with the following: "~~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~~". "**There should be a user requirement document that defines;** **The feedwater quality and expected seasonal variation.** **The water quality required** **The quantity of water required and any other quality requirements – e.g. temperature.** **The system should be commissioned to establish the operating parameters, including the sanitization of the equipment, storage and distribution systems** **Performance qualification should demonstrate reliable operation of the system following defined procedures.**	M	
5.4	145	This section would be made redundant if the suggested text is used.	Suggest deletion: "~~Where production methods other than distillation are used, specific controls should be taken to ensure~~".	L	

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5.4	148	No (i.e., zero) risk is not feasible.	Suggest replacing the text with the following: "~~That there is no risk of contamination of water;~~" "**That the risk of contamination of water is minimized by a thorough risk assessment**".	H	
6.2	161	No (i.e., zero) risk is not feasible.	Suggest replacing the text with the following: "~~There should be no risk of contamination of WFI produced, stored or circulated~~". "**Management of the system should ensure adequate testing of interstage and point of use water; this combined with trending of the test results minimizes any risk of using water not meeting the specifications. Risk controls should include verification that any materials used for maintenance and operation meet predefined specifications**".	H	
6.3-6.5	163	This section would be made redundant if the suggested text is used.	Suggest deletion: "~~An appropriate control strategy should be defined to ensure that all risks identified are eliminated or reduced to an acceptable level~~".	H	
6.6	173	More specific text would help defining the key steps and options – ultrafiltration (UF) should be included double pass reverse osmosis (RO) may not be	Suggest replacing the section with the following text: "~~Techniques such as deionisation, ultrafiltration, water softening, descaling, prefiltration and~~	M	

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		necessary and uses a lot more energy if used when not required.	~~degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a double pass reverse osmosis (RO) system)~~". "**The feedwater quality should be used by a specialist supplier to define the necessary process steps required to deliver water meeting the specifications – where there are options the method selected should be justified – for example softeners can be used or an antiscaling chemical dosing; the softener may be considered more reliable, with the salt required for regeneration easier to source that the antiscaling chemical. For WFI use of combined technologies such as RO+RO/EDI/UF may provide a reliable approach**".		
6.7	177	Add text to ensure all factors are considered in selection.	Suggest revising this section as follows: "~~The~~ **All parts of the system, (pre-treatment, treatment storage and distribution) should be appropriately designed and constructed.** Materials of construction ~~of all parts of the system, including components selected for the production, storage and distribution of WFI systems, should be appropriately designed and constructed,~~ should not be reactive, additive, absorptive or adversely affect the quality of water **and should be suitable for the sanitizing method used**".	M	
6.8	183	Suggest providing more details addressing a whole system.	Suggest replacing the section with:	M	

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			"There should ~~allow for routine sanitisation (thermal or chemical, or a combination thereof). The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals in accordance with a documented procedure~~ **be a defined approach to managing the risk of microbial contamination of the system.** **This may include chemicals or heat for the pre-treatment/treatment equipment. The storage and distribution system is considered self-sanitizing if operated at over 70 degrees C, but control of the use points and any equipment connections should be considered. Use of chemicals may be considered, as well as ozone**".		
6.9	188	Text could be added to address the typical sampling for pre-treatment stages and the "standard" approach to monitoring of a loop.		H	
7.2	198	This section would be made redundant if the suggested text is used.	Suggest deletion: "~~An appropriate method should be used to produce WFI~~".	M	
7.3	200	This text repeats content already in the guideline.	Suggest deletion: "~~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~~".	L	

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7.10	223	The reverse osmosis (RO) is monitored by the conductivity total organic carbon (TOC) instruments required in 7.9 – adding this as a line item may be seen to imply integrity tests (with the associated risk of contaminating the system) are also required – this is not usual industry practice.	Suggest deletion: "~~RO membranes should be monitored for any potential integrity breaches~~".	L	
7.11	225	The text is not clear. We suggest that that periodic review is not required if the system performance is monitored and reviewed.	Suggest replacing the section text with the following: "~~The~~ **To ensure that the** system ~~should~~ remain in a validated state ~~throughout its life cycle~~**;** • **The as built record drawing should be periodically verified** • **An effective change control and non-conformance system should be in place** • **Feedwater quality should be monitored and trended to determine potential impact to downstream final purification steps. Frequency of monitoring should reflect stability of incoming water quality, and at a minimum reflect seasonal variation in source water quality** • **There should be routine trend reports for the interstage water quality and the point of use quality, reviewed by quality**" •	H	
	229 -242	The references would benefit by the addition of a number of useful documents. It would be useful to add section of further reading.	Suggest adding to the references used to develop the document, a further reading section – this could include: "**FDA Guide to the inspection of high purity water systems, 1993**	H	

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			ISPE Baseline Guide: Volume 4 – Water and Steam Systems (Second Edition), 2011 **ISPE Baseline Guide: Volume 5 – Commissioning and Qualification (Third Edition), 2019** **ISPE Good Practice Guide: Commissioning of Pharma Water & Steam Systems (Second Edition), 2014**"		