TABLE FOR COMMENTS

COMMENTS ON WHO WORKING DOCUMENT: QAS/20.842/Rev.1
TITLE OF THE DOCUMENT: GOOD MANUFACTURING PRACTICES: WATER FOR PHARMACEUTICAL USE

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

General comment(s) if any :	**Originator of the comments**
ISPE thanks the WHO for inviting comments on this working document. We offer these general observations for your consideration: To avoid confusion and potentially create additional water categories, we suggest that B Bulk should not be introduced in the water acronyms. We recommend keeping WFI for Water for Injection (in bulk or not) and PW for Purified Water (in bulk or not) rather than BWFI and BPW. For some material standards we suggest using the word Hygienic which is more common in the pharmaceutical industry than Sanitary.	**ISPE**

Section	**Line**	**Comment/rationale**	**Proposed change/suggested text**	**Classification** L= low, M= medium, H= high	**Originator of the comments** (for WHO use)
2.1	125-134	Water is used as well as reagent for QC lab with non-pharmaceutical specifications, and for steam generation used in SIP, we suggest adding these water use in the text.	It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing**), Steam In Place and for QC testing.**	M	

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2.8	167 169 605 769	We suggest using the abbreviation used in all industry and many pharmacopoeias Water for Injection = WFI and Purified Water as PW. Bulk is a status of storage and has no link with the water quality.	Bulk water for injections ~~(BWFI)~~ **(WFI)** Bulk purified water ~~(BPW)~~ **(PW)**	L	
2.8	171-172	We suggest for clarity on lines 171-172 to indicate these uses of WFI are dedicated to sterile products.	WFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied. **The utilisation of WFI is mainly for aseptic processing and Sterile Products.**	H	
3.2	181	We suggest changing the requirement of the capacity to meet minimum and maximum flow demand. This will size the storage vessel .	The capacity of these systems should be appropriate to meet the ~~average~~ **minimum** and peak ~~flow~~ **capacity** demand.	H	
4.2.3	223	If drinking water is supplied from the municipality the control of a continuous positive pressure in the supplying system cannot be ensured by the pharmaceutical manufacturer. We suggest using the proposed addition.	Drinking-water should be supplied under continuous positive pressure **gravity feed** inside **the manufacturing site** by a plumbing system free from any defects that could lead to the contamination of any product.	M	
4.2.9	256	We suggest adding ozone as well as example for decontamination	256 • disinfection or sanitization (e.g. by sodium hypochlorite {chlorine}; **Ozone**);	L	
4.2.10	261	Microbiological contamination cannot be prevented in the pre-treatment part. It can be minimized. We suggest using the term minimize	Controls should be implemented to ~~prevent~~ **minimize** and control microbiological contamination….	M	

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4.2.16	282-283	In the Note – line 211-213 - it is stated that drinking water systems are not usually qualified or validated. The text in line 282-283 is conflicting with this text. We suggest incorporating Risk assessment.	The scope and extent of commissioning and qualification for drinking water systems should be evaluated and justified **where required, based on Risk Assessment.**	M	
4.3.3	304-306	We suggest another format of this clause avoiding making some steps mandatory:	Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare PW. PW may be prepared by, for example, • of ion exchange, • reverse osmosis (RO), • RO/electro-deionization (EDI), • and ultrafiltration. **If required for further production steps.** • Distillation	H	
4.3.4	308-323	We suggest leaving the possibility to make flushing prior to sampling.	• appropriately located sampling points designed in such a way so as to avoid potential contamination**; and the implementation of appropriate operating procedures based on risk assessment.**	L	
4.3.7	336	For a PW production system will "maintaining the water flow at all times" in order to prevent water from stagnating is from a practical point of view difficult. Some systems are operating in "start/stop" mode in order to reduce the environmental footprint for wastewater and CO2. As mentioned in sec. 4.3.5 sanitisation intervals as well as other controls should be defined in order to minimize microbial contamination independent of continuously, no	Maintaining water flow at all times **in the storage and distribution system** is required to prevent water from stagnating.	M	

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		or part time flow. We suggest limiting this close to storage and distribution part;			
4.4.3	365-368	The WFI URS is linked only to distillation, membrane technologies need to be considered as well in the list.	• the optimum generator size or generators with variable control to avoid frequent start/stop cycling; • **The optimum RO and associated purification module size.** • blow-down and dump functions; • cool-down venting to avoid contamination ingress;	H	
4.5	389-392	We suggest clarification of this clause as it is contradictory in the document for non pharmacopoeial grade the water that should meet pharmacopoeia Water for Pharmaceutical Use. We suggest deleting this clause	~~When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within a company's quality system. As a minimum, it must meet the pharmacopoeial requirements relating to the grade of WPU required for the type of dosage form or process step.~~	M	
7.2.1	497-498	We suggest improving the clarity of the document for the text "process stage" – it should be from the main process stage (e.g. RO) – not for a pre-treatment stage (e.g. Softener, Carbon filter)	…. standards up to the **purification** process stage (e.g. RO).	L	
7.2.1	523	We suggest for the surface roughness leaving the possibility having better level.	…surface roughness of 1.0 micron ***or better***…	M	
7.2.1	531-532	We suggest using on-line for TOC and in-line for conductivity and Temperatures	…on-line measurement for total organic carbon (TOC) *and* ***in-line*** *for* conductivity and temperature.	M	
9.2	598-600	For better clarity in this clause dedicated to vessels we suggest considering only jacketed	~~the need for heat exchangers or jacketed vessels~~. Where ~~these~~ jacketed vessels are used, ~~double~~	L	

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		vessels	~~tube sheet or double plate heat exchangers should be used, ideally with~~ the utility pressure should be **lower** ~~less~~ than the system pressure to minimise the risk of contamination **where possible**. **Control system should alert/alarm in case of pressure failure.**		
10.3	615	We suggest clarifying the filtration at point of use for pharmaceutical water systems	Filtration should not be used in distribution loops or at take-off user points **to correct bad practices**. Based on Risk assessment and procedures, terminal filtration at PoU could be allowed.	L	
10.4	617-618	For distribution systems we suggest adding requirements for heat exchangers.	Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system. **Where heat exchangers are used, double tube sheet or double plate heat exchangers should be used, ~~ideally~~ where possible with the utility pressure less than the system pressure to minimise the risk of cross-contamination a control system should be installed**	H	
10.5	620-622	We suggest increasing the scope of this clause.	For self-sanitizing water systems when the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven acceptable during the qualification of the system. For a cold system design with circulation	H	

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			temperature t° below ambient temperature t°, a control strategy with associated alarm and actions limits are required;		
10.7	627-628	We suggest in this clause when a redundant pump is installed, instead of "no dead zone" which is not well defined using no stagnant water should remain.	Where ~~stand-by~~ duty standby redundant pumps are provided, they should be configured or managed and maintained to avoid ~~dead zones dead zones trapped~~ of **stagnant water** within the pumping system.	H	
10.8	630-631	We suggest enhancing the requirement not having stagnant water in as system when it is not in operation.	Consideration should be given to preventing contamination in systems where parallel pumps are used**. *Stagnant water when one of the pumps is not being used should be avoided*.**	H	
12.3	706	We suggest considering use of on-line and in-line terminology. We suggest avoiding off line testing for TOC measures, off line could bring sampling bias which could change the values.	TOC should be monitored with online devices ~~with periodic offline testing to confirm the results~~. Other parameters may be monitored through offline testing.	L	
Further reading	834	We suggest taking care with the Referencing of standard	If ASME BPE is considered as a reference guide then the guideline should match the requirements of ASME BPE. ASME BPE can serve as a source of reference.	H	