EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 November 2016

Submission of comments on ' Q&A on production of WFI by non-distillation methods - RO and biofilms and control strategies' (EMA/INS/489331/2016)

Comments from:

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We are pleased with the change to the monograph to allow production of WFI by alternative methods other than distillation, which allow to use the best available technology while maintaining the quality of the water and keeping the costs of medicines as inexpensive as possible for patients. We welcome the opportunity to comment on this Questions & Answers document. The document as written provides valuable content. It is noted however that it also includes use of technology that has not advanced to the point of being widely accepted and/or useful for monitoring and control of a WFI system. The specific comments below can be supported with data from systems that are currently in operation and/or from publications from industry organizations around the world. The document favours chemical sanitisations, which are not required for maintenance of the water quality in a WFI storage and distribution system based on experience with Pharmaceutical water systems, whether the WFI is made by distillation or by alternative technologies. Use of chemical sanitization can also lead the user to experience contamination events due to improper or incomplete removal of residual chemicals. The use of hot	

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	water sanitisation is the most common proven and effective technique for microbial control with less risk of contamination or harm to personnel performing the task.	
	There seems to be some conflict in terms through the document between “consideration should be given” and “should be included” regarding ozonation and rapid micro methods (see specific examples are listed below). Also it is not always clear where the text is referring to the WFI generation system and where it refers to the distribution system.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 49-59		It seems that the expectation is that RO will be utilised in an alternative WFI system even if the feed stock is PW. As an alternative approach a CEDI unit coupled with Ultrafiltration would give both chemical and microbial separation from the PW feed and mitigate the risk posed by biofilm formation in the RO. Proposed change (if any):	
Lines 76-78		Comment: It is not necessary to routinely steam or chemically sanitise storage and/or distribution systems. Proposed change (if any): The distribution and storage systems should be designed to permit sanitisation and in accordance with other good design practice to minimise areas of reduced flow. Thermal approaches to sanitisation include periodic or continuously circulating hot water. Chemical sanitisation techniques can also be effective however they require additional considerations such as appropriate material of construction selection and sanitisation agent removal techniques or equipment. Ozonation may also be utilised.	
Lines 83-84, 176, 366		Comment: Lines 83/84 and 366 state use of ozone **should be considered**. This contradicts line 176 which states that	

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		ozonation should also be incorporated. Proposed change (if any): Ensure adequate removal of organic particles and microbial impurities. Use of ozone may be considered as it is a powerful antioxidant that controls microbial growth and reduces the concentration of organics due to oxidation.	
Line 87		Comment: The typical approach is to use a softener which is a specific ion-exchange method that is targeted to control scale by removal of hard ions like Calcium and Magnesium. Proposed change (if any): Control of scaling – usually controlled by use of ion exchange softener upstream of membrane.	
Lines 94-95, 97-98		Comment: “Free Chlorine” is mentioned, and no mention is made of chloramines. Chloramines are harder to remove, and are becoming the prevalent form of chlorine, at least in North America. Proposed change (if any): Oxidizing agents such as Total Chlorine, Free Chlorine, Chloramine (combined chlorine), chlorine dioxide, hydrogen peroxide, ozone, and permanganate will damage membranes, if not properly removed or reduced before entering the RO. Activated Carbon units are commonly used to absorb the oxidizing agents but	

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		these carbon units must be routinely replaced and the units routinely sanitised for microbial control. Sodium metabisulfite is also commonly used to chemically reduce the oxidizing agents.	
Line 96		Comment: ORP is used to measure free chlorine but the sensors often age poorly or respond slowly. There are commonly used chlorine electrochemical sensors too. Auto-titrators can provide superior performance if maintained properly. Proposed change (if any): The monitoring of oxidizing agents prior to the RO is recommended. Detection methods include oxidant-reduction potential electrodes (ORP), instruments using electrochemical sensors, and auto-titrators, each having benefits and limitations.	
Lines 99-103		Comment: Deionization pre-RO is rarely, if ever, used. Post RO, yes. Another method commonly used pre-RO (and between RO stages) is pH adjustment to improve rejection efficiency. Spelling of nanofiltration is incorrect. Proposed change (if any): Pre-treatment of water is essential in order to minimise the impact to the RO membranes. Techniques such as deionisation, water softening, descaling, pre filtration, degasification (can be located between the stages of a double pass RO system), pH adjustment (can be	

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		pre-RO or between the stages of a double pass RO system), nanofiltration, electro-deionisation, ozonation, UV treatment and micro-filtration should all be considered during the design phase to assure the quality of the water produced.	
Lines 110-113		Comment: It is not possible to sanitise RO membranes at 120C. Most manufacturers limit the temperature to a maximum 85C, therefore the hold threshold from a validation perspective would be 80°C. It is not necessary to design for technology that does not exist at this time. This situation would need to be evaluated through change management if/when technological advances are made. Proposed change (if any): End this paragraph after "routine chemical sanitisation" in line 110.	
Lines 116-117		Comment: WFI quality water can be produced with a single pass RO. Double pass RO would be just one of many technologies that could be used. Proposed change (if any): Delete this statement	
Lines 121-123		Comment: Disagree that the microorganisms are difficult to remove by standard techniques. Hot water sanitisation and flushing is very effective. Chlorine-resistant membranes are not necessary or required post RO. Per the statements above oxidizing agents must be removed prior to the RO or	

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		membrane damage will occur. Proposed change (if any): Microfiltration(MF)/ultrafiltration(UF) offers advantages in that it can remove microorganisms therefore these systems should be designed to allow for routine sanitisation such as with hot water and flushing.	
Lines 125-136		Comment: TOC “meters” is an out-of-date term and inaccurate and it would be better referred to as TOC instrumentation. This section states that online TOC instruments are required to monitor WFI made by RO. This is not required in the monograph. TOC measurements have value and could be considered as part of the overall control strategy but it is not required. This technology will allow continuous monitors, such that one can act upon those measurements to determine if upstream processes require investigation or adjustment. Additionally a line needs be added to advise that data should be routinely reviewed and appropriate action be taken to adverse trends. Additionally, TOC monitoring of the feed water is expensive and of little value since the user has no control over the level of TOC provided by the municipality. This information is typically available from the municipality. Proposed change (if any): Change line 125 to read "On-line TOC instrumentation may be employed as part of the control	

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		strategy and located at various . . ." Line 129 needs be supplemented with "This information may be available from the municipal supplier if the water is sourced from a municipality." Add line stating “Routine review of the TOC data is required with appropriate action to adverse trends or when out of control signals are detected”	
Lines 138-142		Comment: Systems should be designed to allow for diversion of water that does not meet TOC requirements after the final treatment step, but this diversion may not require automation. Additionally, the location of this statement may imply that TOC instruments, at all of the suggested locations listed above the statement, should also be designed for diversion and require documentation in the Pharmaceutical Quality System. Proposed change (if any): Rewording suggestion "System design should be such that there is an option to divert through a recirculation system back through part or all of the treatment process or to drain when the quality of the final water produced is outside the acceptable limits. This should also result in reporting under the Pharmaceutical Quality System so that the frequency of such excursions can be monitored and the root cause investigated appropriately."	
Lines 147-148		Comment: Alert limits, by definition, are based on historical	

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		data from the system and may increase or decrease based upon system performance. These statements imply that it is acceptable to tighten these limits based on performance but not to relax the same limits based on performance. Proposed change (if any): please clarify further or delete the last two sentences in this section.	
Lines 151-156		Comment: Conductivity “meters” is an out-of-date term and is now referred to as conductivity instruments. This section states that online conductivity instruments are required to monitor WFI made by RO. This is not necessary, but could be considered as part of the overall control strategy for the WFI system. It is also not required in the monograph. Proposed change (if any): Rewording to read "On-line conductivity instruments may be employed as part of the control strategy and located at various locations within the RO system. The location of these devices should take in to account the locations specified above under TOC. Consider monitoring the conductivity of the RO permeate in order to aid with determination and trending of membrane performance. An increasing trend in permeate conductivity can be an indication of membrane degradation, seal failure, or improper pH control." A statement similar to "Increases in feed or differential pressure across the membrane are indicators of increased scaling or fouling." could be relocated to a more	

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		appropriate section of the document as it is not related to conductivity and is misplaced in this section.	
Lines 166-174		Comment: Periodic hot water sanitisation or operation at a continuously sanitising temperature of 65C or higher is sufficient to achieve microbial control in a WFI system. Please note that the list of sanitizing agents may be misleading because some of them must be used together to avoid oxidizing/damaging the membranes. Sodium hypochlorite should not be used to sanitise polyamide RO membranes. This will damage membranes. Line 169-170: The terminology here should be chemical clean, i.e. acid/base clean to remove residues from the R/O membranes and routine thermal sanitisation. If thermal sanitisation is demonstrated to give good control then routine chemical sanitisation should not be necessary Proposed change (if any): Rewording as "The system should be designed for periodic or continuous sanitisation at a temperature of 65C or higher. RO membranes that can withstand high temperatures are currently available and should be utilised in order to allow for routine high temperature flush of the system in conjunction with periodic chemical clean. Use of sanitizing agents such as peracetic acid in conjunction with hydrogen peroxide, the use of dilute sodium hypochlorite, continuous ozonation or other	

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		compatible agents should be considered as part of the control strategy for the RO purification step."	
Lines 176-183		Comment: Ozone is not the only method that can be used for microbial control. This section seems to cover also pretreatment and distribution parts of a water system. Proposed change (if any): Could remove this section or repeat wording from other sections of the document. See suggested wording for lines 166-174 with regard to RO unit sanitisation. For distribution system sanitisation, see the suggested wording for lines 76 to 78.	
Lines 184-195		Comment: Biofilms on RO membranes cannot be detected without destructive inspection, so it is not clear how one can confirm the absence. Water sampling alone is insufficient, as low level of biofilm may not lead to positive bioburden in water samples. Proposed change (if any): RO membranes time-based lifetime should be established. Qualification should consider destructive analysis of RO membranes to ensure the absence of biofilm, or any surface that cannot be visually inspected regularly.	
Lines 200- 206		Comment: It seems that the expectation is that RO will be	

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		utilised in an alternative WFI generation system even if the feed stock is PW. See comment for lines 49/59. Proposed change (if any):	
Lines 218–219, 379-381		Comment: Sampling daily from each POU used that day may be excessive and is not necessary to demonstrate satisfactory continued performance of the system particularly if the system is a hot storage and distribution system. Proposed change (if any): Sampling points and frequency should be based on validation data and water usage.	
Lines 225 - 239, 390		Comment: 225 states: use of rapid methods **should be employed as a prerequisite**. This contradicts 235 which states: use of rapid micro methods should be given **due consideration**. 238 and 390 also state: rapid methods **should be employed.** The current rapid micro technology available may not be robust enough compared to traditional methods. Current online microbial testing is destructive and precludes subsequent isolate identification. Additionally, the equipment can only confirm the presence of bacteria with a size of greater than or equal to 0.5 um. This size limitation does not allow for the detection of many significant genera of bacteria (i.e. Mycoplasmas), and may result in differences in the results obtained by rapid microbial methods compared to	

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		traditional grab sample monitoring using agar plates. Will there be guidance about required limits if a rapid microbial method is used? Routine isolate identification is a requirement of all of the major pharmacopoeias, and rapid microbial enumeration is not currently compatible with identification. Rapid endotoxin technology also has limitations that make it inferior to grab sample monitoring at this time. Additionally, will the descriptions of rapid microbial and endotoxin testing be applied to WFI made by distillation, or are the statements unique to WFI made by RO? Would it be required to perform both rapid methods and traditional methods, or one of them would be sufficient? Ph. Eur 5.1.6 does not currently provide clear guidance on rapid endotoxin methods. Proposed change (if any): This section should focus on sampling WFI made by RO in a way that is similar to sampling WFI made by distillation (i.e. grab samples for microbial and endotoxin). A discussion of rapid microbial sampling is appropriate, but should include information about the current limitations while encouraging its use in the future if the technology improves. A statement like "Rapid microbial monitoring equipment is currently available,	

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		but is limited to organisms greater than or equal to 0.5 um and is a destructive test, which precludes isolate identification. This renders this technology of limited use in the monitoring of a pharmaceutical water system at this time, although advances with this technology may make this a suitable technology in the future." A similar statement about rapid endotoxin monitoring and its limitations could also be included.	
Lines 342-358		Comment: There are many methods for biofilm inactivation and removal. The discussion in this section includes a way to perform removal, but states it as the only way to perform removal and not just an option. Additionally, the statement in lines 357 and 358 about intensive monitoring after removal and before returning the system to service may not be necessary if the method of removal is robust and already proven. Proposed change (if any): Rewording to: "The approach to biofilm removal may vary depending upon the complexity of the system and the severity of the biofilm formation. Use of chemical sanitizing agents is an effective method for biofilm removal but introduces the risk of residual chemicals remaining in the water system. Appropriate velocity during flushing will aide in the removal of debris and chemicals.	

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		Thermal inactivation can also be an effective way to inactivate a biofilm, but this method will typically require repeated and/or extended elevation of temperature compared to the routine sanitisation cycle."	
Lines 346-349		Comment: Not clear if this section refers to generation system or storage and distribution or both. Proposed change (if any):	
Lines 356-358		Comment: The intense monitoring does not specify a trend of acceptable water quality before returning the water system to service. The remediation should return water quality to the same level as the initial qualification. Proposed change (if any): Any biofilm removal should be followed by a period of intense monitoring before returning the system to use to ensure that the biofilm has been effectively removed, and water quality is consistent with the initial qualification.	
Lines 364-365		Comment: Routine passivation chemistries have proven to be effective at also removing biofilms. This paragraph might also include a statement to this effect. Proposed change (if any): Adding a statement encouraging the use of the users' preferred passivation chemistry.	

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Lines 368-371		Comment: This statement may not be accurate in our experience. A singular approach should be acceptable for a system that is maintained continuously hot…there is simply no opportunity for biofilm to even appear. Proposed change (if any): make exception to continuously hot systems.	
Lines 389-391		Comment: Because of the limitations discussed in the comments for lines 225-239, this paragraph could be deleted. Proposed change (if any): Deleting this paragraph.	

Please add more rows if needed.