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4 November 2016

EMA
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RE: EMA/INS/GMP/489331/2016 GMP/GDP IWG
Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Dear Sir/Madam:

PDA appreciates the opportunity to provide feedback on this draft and fully supports the implementation of non-distillation methods for WFI production into the European regulatory framework. In addition, PDA endorses the premise that non-distillation technology for producing WFI should produce water equivalent in quality to that produced by distillation. However, PDA has concerns with many of the approaches specified in this Q&A that are not science and risk based, some of which set requirements above and beyond what is in the Pharm. Eur. Monograph.

PDA recommends referencing existing technical documents for best practices and allowing manufacturers to make science and risk based choices rather than limiting the possibilities by writing overly prescriptive regulatory guidance or monographs. In addition the requirements for distribution and storage systems should permit manufacturers a choice of routine sanitisation approaches such as steam, hot water, ozone or other chemicals and not require redundant approaches or steam in all cases.

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 with expertise in pharmaceutical water systems representing the Science Advisory Board, the Board of Directors and including authors of PDA Technical Report 69 *Bioburden and Biofilm Management in Pharmaceutical Manufacturing Operations*.

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

Sincerely,

Georg Roessling
Vice President, PDA Europe

CC: Simona Keckesova, EMA; Richard Johnson, PDA; Denyse Baker, PDA

<4 November 2016>

EMA/INS/GMP/489331/2016 Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Comments from:

Name of organisation or individual
Parenteral Drug Association

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Critical Comment (Y/N)?	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment		Decision to Submit/ withdraw comment
	PDA fully supports the implementation of non-distillation methods for WFI production into the European regulatory framework via a monograph and updates to Annex 1 and endorses the premise that non-distillation technology for producing WFI should produce water equivalent in quality to that produced by distillation. However, PDA has strong concerns with many of the approaches specified in this Q&A that are not science and risk based, some of which set requirements above and beyond what is in the Pharm. Eur. Monograph. PDA recommends referencing existing technical documents[1][2] for best practices and allowing manufacturers to make science and risk based choices rather than limiting the possibilities by writing overly prescriptive regulatory guidance or monographs. Examples are rapid micro methods and on line vs. off line TOC methods[3]. This document should clarify monitoring methods which are reactive vs. control methods which are proactive. In addition the requirements for distribution and storage systems should permit manufacturers a choice of routine sanitisation approaches such as steam, hot water, ozone or other chemicals with appropriate justification and not require complete redundant approaches or steam in all cases. Generally, PDA comments that the use of the word “should” is perceived		

[1] PDA Technical Report No. 69: Bioburden and Biofilm Management in Pharmaceutical Drug Substance Manufacturing, PDA, Bethesda, 2015
[2] Position paper “Reverse Osmosis as a Means of Water For Injection Production: A Response to the Position of the European Medicines Agency” published in the PDA Journal of Science and Technology January 2009, Volume 63
http://journal.pda.org/content/63/1/1.full
[3] PDA Technical Report No. 33: Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods PDA, Bethesda, 2013

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Critical Comment (Y/N)?	Outcome (if applicable) *(To be completed by the Agency)*
	as an indication of “a must” requirement. In the context of this Q&A approach, PDA recommends the use of word “may” throughout the document as it allows practitioners to utilize risk based scientific approaches. Furthermore, the document also perpetuates the misperception that microorganisms can build up a resistance to disinfectants, and, as such, disinfectants should be rotated on a routine basis or else risk a growth of a highly-resistant organism. PDA recommends referencing pivotal evidence or illustration for this assumption. Rotation of a disinfectant and a sporicide is sufficient to significantly reduce the microbiological flora in a water 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')*	Critical Comment (Y/N)?	Outcome *(To be completed by the Agency)*
Q2 51-54		Comment: There is no mention of chemical contamination such as ionic contaminants. Inorganic and organic materials are also important contaminants removed by RO. Proposed Change: …relate to the microbiological **and chemical** quality of the water…		
Q2 53-54		Comment: In PDA's opinion, the statement about detection leads to unnecessary implications. There continues to be no evidence that microbial toxins exist at any detectable level and no evidence that those undetectable levels are actually toxic. Proposed change (if any): Delete this phrase	Y	
Q2 55		Comment: It is not only the ambient temperature but the materials of construction in the RO membranes and the inability to sanitize using harsh chemicals. Proposed change (if any): …operate at ambient temperatures **and are only chemically sanitizable** offer an ideal environment…	Y	
Q2 58-59		Comment: For clarity PDA recommends it would be helpful to name the by-products that are being discussed. Proposed change (if any): …increasing the likelihood of microbiological by-products throughout a system **such as endotoxins.**	Y	
Q3 74-75		Comment: Pre-treatment materials of construction are of lesser concern due to subsequent treatment processing. The variation of incoming water would make materials compatibility testing at earliest stages unnecessarily challenging. Proposed Change: The materials of construct for the **final stage of**		

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		treatment ~~generation~~ and distribution systems must not be reactive, additive or absorptive to such an extent that it will **adversely** affect the quality of water produced.		
Q3 76-77, 166, 176-181; Also Q5 366		Comment: The design features to allow steam use presented as requirements in this document create greater risk of contamination between steamings than a simple hot water sanitization would (e.g. no low point steam traps or steam injection points needed which could become dead legs in a water system) HW sanitization of RO is adequate as is HW sanitization of storage and distribution. Steam sanitization of storage and distribution is unnecessary, since biofilm-forming organisms in a water system are extremely susceptible to hot water temperatures (D value of 5 millisec at 80C). Proposed Change: The distribution and storage systems should be designed as to permit routine ~~steam~~ sanitisation **by steam, hot water**, **ozone or other** ~~with routine~~ chemical**s** ~~sanitization~~ and in accordance with other good design practice.	Y	
Q3 83-86		Comment: There are numerous technologies available for water pre-treatment, each with advantages and disadvantages. Ozone is not appropriate for use in the generation portion of a system based on current materials technology. Ozone application for storage and distribution must address materials compatibility. The guidance should provide allowances for the many possible technologies. The serious downsides of ozone are material incompatibility and relatively slow reactivity for organic degradation all the way to CO2. Ozone pretreatment is more likely to create AOC which will encourage greater biofilm development in the RO, not less. If organics, particles and microbial impurities are a problem, alternative solutions are depth filters, UF, micro-filtration, organic scavenger resins, and even well-maintained activated carbon beds.	Y	

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		Proposed change (if any): • Ensure adequate removal of organic particles and microbiological impurities. **The** use of ozone **may** ~~should~~ be considered as it is a powerful ~~anti~~oxidant that controls microbial growth and reduces the concentration of organics due to oxidation.		
Q3 87		Comment: The term ion exchange could be mistaken to mean something more complex and unnecessary at this stage. Proposed change (if any): Control of scaling – ~~usually~~ **typically** controlled by use of ~~ion exchange~~ softening **or appropriate technology** upstream of membrane.	Y	
Q3 94		Comment: There are a number of methods for reducing chlorine and chloramines. The removal of chloramines, in particular, should be highlighted; RO membranes do not effectively reject chloramines. Proposed change (if any): …activated carbon, ~~or~~ chemical reducing agents such as sodium metabisulfite (SMBS) ~~commonly used for removal of free chlorine and as a biostatic~~, **or other suitable technologies.**	Y	
Q3 96		Comment: ORP is used to measure free chlorine. However, there are commonly used chlorine electrochemical sensors too. Proposed change (if any): Residual free chlorine can be detected with oxidant-reduction potential electrodes (ORP) **or other methods.**		

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Q3 100		Comment: Although PDA agrees that pre-treatment is essential, we disagree with suggested use of deionization pre-RO. 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 … should all be considered during the design phase to assure the quality of the water produced. **Another method commonly used pre-RO (and between RO stages) is pH adjustment to improve rejection efficiency.**		
Q3 116 & 117		Comment: The use of double pass RO should not be required but considered based on local conditions. Technical opinions differ on whether maintenance is improved. Proposed change (if any): Use of Double pass RO membranes ~~should~~ **may** be considered **based on feedwater analysis** as an added assurance ~~of the maintenance~~ of the quality of the water produced.		
Q3 123		Comment: Chlorine resistance should not be a necessary prerequisite for membranes. There are other—highly effective—antimicrobial agents (peracetic acid/hydrogen peroxide) that can be used for membrane treatments. Proposed change (if any): The MF/UF membranes should be made from ~~a chlorine-resistant~~ **materials that can** ~~material to~~ withstand periodic sanitisation.	Y	
Q3 125 - 126 and 151		Comment: Online TOC monitoring is not required per the current monograph (in-process monitoring for conductivity, “regular monitoring for TOC and microbiological quality) so should not be stated as a requirement in this Q&A. TOC “meter” is no longer current technology.	Y	

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		Proposed change (if any): Online TOC ~~meters~~ **instrumentation may** ~~must~~ be employed to support the control of the RO water system. The location of ~~on-line~~ TOC **sampling** should be based on risk assessment.		
Q3 138-139		Comment: The guidance indicted that water must be recirculated for reprocessing. Proposed change (if any): The guidance should allow an option to discard water not meeting specification.	Y	
Q3 143 - 144		Comment: There should be a back-up plan for any automated system. There is no need to call out on-line TOC specifically. PDA recommends that this requirement is more appropriate for a validation document. Proposed change (if any): Delete this line.		
145-148 and Q6 240-243		Comment: In PDA's opinion the term "alert limit" can be commonly misinterpreted and recommends using terms from Ph.Eur. Proposed change (if any): Appropriate **process control levels such as** alert **and action levels** ~~limits~~ should be established…		
159		Comment: As written this sentence seems to refer to failure of measurement system and not to when conductivity systems detect failing water. Proposed Change: When on-line conductivity systems **detect water out of specification** ~~fail~~, robust corrective measures should be put in place that will assure…		
164-165		Comment: Microbiological flora do not become resistant to thermal / chemical / mechanical methods of cleaning and sanitization. Possible resistance and rotation of disinfectants is not proven as a requirement		

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		for microbiological control. References should be added to support this statement or it should be deleted. Proposed change (if any): delete lines 164 and 165.		
166 - 179		Comment: Hot water and ozone, in addition to steam, have been shown to be effective sanitizing agents. This document should allow for risk management in selection of an appropriate sanitization regime. It may not be necessary to have multiple, redundant approaches in a single system. Proposed change (if any): The system should be pressure rated appropriately for the ~~to enable routine steam~~ **selected method of** sanitisation ~~throughout the distribution loop and storage tanks.~~	Y	
176-181		Comment: Again, ozonation can be an effective system treatment and there can be advantages to storing water (at ambient temperature) with an ozone residual. However, ozone's use should not be specified without including caveats. The paragraph also notes that "…it is unlikely that a distribution system with non-stainless steel components would be acceptable."; however, this is a false statement. Many systems have been built with polymeric components that are both ozone and heat/steam compatible. Proposed change (if any): The use of ozone should be included as an option for sanitization.	Y	
178-9		Comment: The semiconductor industry successfully using high end plastics for distribution systems - ETFE, ECTFE. Stainless steel is not required.		

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		Proposed Change: Remove this line. ~~Usually, stainless steel is employed; it is unlikely that a distribution system with non-stainless steel components would be acceptable.~~		
Q4 184-195		Comment: PDA recommends that there should be no less or no more rigorous validation requirements for an RO WFI system as compared to any other WFI technology. The approach should be risk-based, scientifically justified and appropriately demonstrated. Proposed change (if any): Rewrite this section with principles as noted here.		
Q4 192-193		Comment: The statement "should be extended" is neither clear nor justified. Extending duration of the initial sampling phase of validation beyond the normal time for all water systems would be inappropriate for an RO technology system. Typically 4-6 weeks of initial frequent testing period is sufficient. Proposed Change: The initial validation period of the water system where testing is carried out on all points should ~~be extended to build~~ **demonstrate** confidence that the system is operating as designed.		
Q5 208-219		Comment: Routine monitoring of RO WFI systems should not be different than for distillation WFI systems. The sampling approach to an RO system should be equivalent to sampling for any other WFI system to ensure validation is properly executed. Any specific additional sampling should be determined with a risk based approach considering the RO design or installation. Proposed Change(s): Line 208-210 …the above points should be sampled and tested **frequently** ~~daily~~ for a specified period of time …. Line 212 - The sampling frequency should be designed in a **risk based** manner". Delete lines 218-219.	Y	
Q6 234		Comment: PDA recommends test methods beyond just microbial should be considered such as Conductivity and TOC.		

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		Proposed change (if any): Add new bullets **Conductivity and Total Organic Carbon**		
Q6 225 – 229; 238-239 (See also 389-391)		Comment: PDA agrees with the reference to Ph.Eur. 5.1.6 and believes That this document should not mandate the use of RMM above and beyond the Ph.Eur. monograph requirements. Proposed change (if any): Use of rapid microbiological methods ~~should be employed as a prerequisite~~ **could be advantageous** Also delete 238-239.	Y	
Q7 252		Comment: The use of defined frequency does not take into account performance based approaches to preventive maintenance. Proposed Change: …defined frequency, **based on system performance,** or following adverse indicators …	Y	
PART II Q1 Line 260; 273-295		Comment: This entire section seems to be out of context in this document and more academic than what is necessary for purposes of design, validation or control of the water system. PDA recommends that this document referred to other more detailed information on biofilms such as existing industry technical reports. Proposed Change: Delete information following 273 through line 295.	Y	
Par II Q1 296 - 300		Comment: PDA believes that planktonic organisms can be detected by appropriate sampling approaches. More planktonic organisms detected may be an indicator of greater biofilm. Grab samples should be collected in the same fashion as the water is used. . Individual pioneer cells that are randomly released from the system biofilms occur, in a steady state so routine sampling at sample ports should recover these types of organisms. Proposed Change: Current methods of control of bioburden are based on **appropriate system design and sanitization practices**. **Subsequently the follow up** ~~control~~ **monitoring** of the **levels** planktonic organisms present **is an indicator of the efficacy of the**	Y	

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		control measures…. They can be difficult to identify within a system / process as their presence is usually relatively unknown until such time **as a process control indicator excursion** ~~as an out of specification result~~ occurs.		
Part II Q3 333		Comment: This statement is not clear, "They are typically assessed and monitored in isolation." A robust quality system will not monitor these in isolation but will use an integrated approach. Proposed change (if any): Delete the sentence;		
Part II Q4 342		Comment: Physical removal has a high risk of damaging the surface leading to higher rate of potential recolonization and corrosive attack(rouging in the case of stainless steel) and should be used with caution, if at all and taking into consideration where the problem lies within the system.. Proposed change (if any): "The **preferred** approach is ~~both~~ chemical. **Any** physical removal **approaches should be used with caution because of the high potential of damaging the surface leading to higher risk of recolonization and/or corrosive attack (rouging in the case of stainless steel).**		
Part II Q4 342-345		Comment: Implies all portions of the system must be recirculated and recirculation is required for sanitization. A recirculation mode requires major changes to design and installation requirements. Having a "mode" is not necessarily required. For example, steam would not be recirculated. Proposed Change: When ~~sanitising systems in this manner~~ **hot water or chemical sanitants are being used**, it is important to ensure that the systems are ~~in~~ recirculat**ing or flowing whenever possible** ~~mode~~ and the sanitising agents utilised….		

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')*	Critical Comment (Y/N)?	Outcome *(To be completed by the Agency)*
Part II Q4 346		Comment: There is no evidence to indicate that hot water flushes are ineffective against biofilms. To the contrary, both hot water and steam, when used at appropriate temperatures/contact times/frequencies, are effective sanitizing agents. Neither agent, however, will necessarily remove non-viable bacteria or biofilm components. From a risk based standpoint, it is better to keep chemicals out of the system wherever possible. Chemical sanitizers poorly penetrate into nooks and crannies where biofilms can sequester, not be killed by those agents which can't reach them, then serve to re-inoculate the entire system. Some sanitizers can degrade exposed biofilms and kill the cells within, but it is the sequestered locations where chemical sanitizers fail to kill (e.g., around gaskets, O-rings and seals). Heat penetrates primarily through conduction to these locations and kills the biofilms there. Proposed change (if any): Use of chemical sanitising agents should be ~~incorporated~~ considered as part of ~~into~~ **an effective** control strategy.	Y	
Part II Q4 347 - 349		Comment: Heat does kill biofilms. The issues are: 1) Establishing sufficient treatment times to allow all the cold spots to achieve the necessary temperature for the necessary time. 2) Heat does not remove biofilms dead or alive. Proposed change (if any): it is known not have a significant effect on **removing killed** biofilms. ~~which typically do not exist in a planktonic form, but usually in a sessile or attached form.~~	Y	
Part II Q4 350-351		Comment: Biofilms must be removed not only killed. Proposed Change: The ideal mode of action of chemical sanitising agents in the context of biofilm is to ~~both~~ penetrate, ~~and~~ provide the appropriate kill to the organisms in question **and remove the dead biomass.**		

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Part II Q4 354-355		Comment: There is no evidence that water system chemical agents used at the recommended use dilutions induce antimicrobial resistance. There is no evidence that rotation is needed. The use of sporicidal agents should not be implemented in the absence of the presence of spore-forming bacteria. Use of these agents can create health, safety, and environmental/disposal challenges. It is not recommended to ever use a 'detergent' in a water system because characteristics of the surfactant may never be able to removed. Proposed change (if any): Delete.	Y	
Q5 364		Comment: PDA suggests that alkaline cleaning agents (NaOH or KOH) should be added as examples. Reference is PDA Technical Report69 (6.3.2.1) states Proposed Change: Examples include **Sodium Hydroxide, Potassium Hydroxide,** Sodium Hypochlorite, Hydrogen Peroxide		
Q5 368		Comment: When operated correctly, a single approach could be completely effective in controlling biofilm. Having a secondary approach may be advantageous but should not be required. Proposed Change: Having a **secondary** approach to sanitisation **may be advantageous** ~~is not an acceptable approach~~ in order to minimise the risks of biofilm formation. ~~In that regard an approach that utilises a minimum of a double-edged approach should be considered,~~	Y	
Q6 379		Comment: This sentence is unclear as it could imply that a system would only be tested on days when production is in operation or testing each outlet every time any outlet is used. Water quality is best assessed through a pre-determined, systematic approach. Proposed Change: Delete the sentence ~~User points should be tested each day of use in order to provide additional assurance of the quality of water utilised in the manufacturing processes~~.		

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Q6 385-387		Comment: The sensitivity of endotoxin methods is not adequate to detect levels of biofilm that are more easily detectable by microbial counts. In addition the detection of endotoxin at a given location is not necessarily an indicator of local biofilm presence, but that could have come from far upstream. Proposed change (if any): Delete paragraph.	Y	
Q6 389-391 (see also 225-229; 238-239)		Comment: The statement "speed at which organisms can proliferate" implies growth beyond what is realistic. RMM is not necessary to control a water system. This document should not mandate the use of RMM above and beyond the Ph.Eur. monograph requirements. Proposed Change: ~~Taking into account the speed at which organisms can proliferate,~~ **T**he use of rapid microbiological test methods and systems ~~should~~ **may** be employed in order to improve or increase the probability of early detection and allow timely action to be taken.		

Please add more rows if needed.-