<03.11.2016>

Submission of comments on

['Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211657.pdf) '

(EMA/INS/GMP/489331/2016)

Comments from:

| Name of organisation or individual |
| --- |
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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)* |
| --- | --- | --- |
|  | EFPIA and EBE appreciate the opportunity to comment on this draft Q&A on WFI water production by non-distillation methods. The content of the Q&As and the clarifications it supports are highly appreciated.  We acknowledge the industry responsibility for taking account of scientific and technical progress.  However, forcing new progress into current well performing systems should be done with both cost and supply of medicines in mind.  EFPIA and EBE would like to raise 3 main concerns:   1. The scope of the Q&A encompasses production of water for injections by non-distillation methods, not storage and distribution systems. Only water treatment systems should be part of this document. 2. The mandatory call for use of rapid microbial methods 3. The mandatory design of RO systems to encompass the possibility for future potential sterilisation methods not invented yet. |  |
|  | Although the concerns for microbial growth in the RO production system are clearly understood, it is not seen how this affects the performance of the storage and distribution systems. Therefore the requirements on the control and monitoring of the storage and distribution systems should not be differentiated based on the production method (distillation or reverse osmosis). The sanitisation methods should be implemented on a risk based approach.  The practice of using thermal sanitisation methods (e.g. hot water) is well described in many regulatory guidance documents and we would like to recommend to the agency to maintain this industry practice.  Distribution systems pertain to more than non-distillation methods for WFI and should be discussed outside this document. |  |
|  | The document appears to be mandating the adoption of new technologies such as rapid microbiological methods. Currently there is no consensus whether these systems are suitable for the monitoring of WFI systems. While the instruction to explore and adopt new technologies is to be encouraged, it is premature to make this mandatory. |  |
|  | Generation of WFI by distillation requires basically the same techniques of feed water treatment as described in this document. This could unintentionally lead to the conclusion that all requirements described in this document might be also applicable to those techniques of feed water treatment in distillation systems. To avoid any misinterpretation, the document should clarify what the author’s or agencies’ stand regarding this aspect is. |  |

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|  | It appears that the level of control, security and preventive method for contamination are by far more stringent than the ones required for the WFI produced by the distillation method. It gives the impression that EMA considers this WFI production method as more risky and will raise questions and potential concerns from inspectors.  As most of the purification steps for cold and hot WFI generation are the same (e.g. softener, reverse osmosis) the requirements for the level of control, security and preventive method for contamination should also be the same.  Overall, the foreseen rigor on control strategies will hamper the installation of such systems in the pharmaceutical production environment. |  |
|  | The understanding of the guidance is that it applies to new systems. Retrospective application of the guideline is not recommended if current water systems are performing appropriately when assessing system trends and water quality meets the specification.  It is also understood that the additional control methods are not applicable to WFI produced by distillation or for Purified Water systems although those systems also use reverse osmosis in the preparation chain (pre-treatment phase). |  |

1. 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)* |
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| Lines  6-7 |  | Comment:  The statement “The Ph.Eur.monograph (Monograph 169) was revised to include, in addition to distillation, reverse osmosis (RO) coupled with suitable techniques, for the production of WFI.” does not precisely reflect the requirements in WFI monograph 169.  The monograph states “Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable.”  Proposed change (if any):  The Ph.Eur. monograph (Monograph 169) was revised to include a suitable purification process which has been proven being equal or superior to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. |  |
| Line  65 |  | Comment: The following section should be clarified:  *“A robust control strategy should be developed in parallel with the design considerations*.” to state that the control strategy should be documented.  Proposed change (if any):  *A robust control strategy should be developed and documented in parallel with the design considerations.* |  |
| Lines  76 – 78 |  | Comment:  The requirement for routine steam sanitisation and routine chemical sanitisation seems excessive for the distribution and storage system. The routine use of one method should be sufficient, if validated.  Hot water sanitisation is also a common and widespread method for the sanitisation of WFI systems.  Proposed change:  Re-phrase to read: “….to permit appropriate thermal sanitisation (steam or hot water)~~along with~~ or routine chemical sanitisation….The usage of additional sanitisation methods besides the routine sanitisation should be based on system performance. Or delete lines as they are part of the distribution system and therefore they should not be reflected in this document. |  |
| Lines  99 - 107 |  | Comment:  These two paragraphs are repetitive and could be combined.  Proposed change (if any):  Pre-treatment of water is essential to ensure that the feed water will be of an adequate quality for a final treatment step, thereby protecting the membrane, minimising membrane degradation and aid with minimising the risks associated with microbiological proliferation and biofilm formation. Techniques such as deionisation, water softening, descaling, pre-filtration, degasification (can be located between the stages of a double pass RO system), nanofiltration, electro-deionisation, ozonisation, UV treatment and micro-filtration should all be considered during the design phase to assure the quality of the water produced. |  |
| Line  107 |  | Comment:  Delete RO  Proposed change (if any):  The quality of feed water should be monitored. |  |
| Lines  99 -123 |  | Comment:  Electro-deionisation has no endotoxin reduction capability.  Microfiltration (MF) cannot be considered as an option for downstream RO to generate BWFI because it has no capability to remove endotoxins (unless limited application of positively charged filters).  Nanofiltration has not been validated by any manufacturer/supplier data related to endotoxin retention capability. Only ultrafiltration has manufacturer/supplier data proved/validated related to endotoxin retention capability.  Proposed change (if any):  “Additional techniques coupled with these further techniques post RO membrane should be considered such as ultra-filtration (known to have an endotoxin reducing capability).” |  |
| Lines  108-113 |  | Comment:  Further development is highly speculative. Recommendations should focus on the state of the art and not on the state of research. In addition, high temperature sanitization would be not the only way to control microbial growth. Systems such as HERO operate at elevated pH (>10) which control microbial growth without the need for high temperature sanitization.  If a system is in use and under control for a long time with validated sanitization procedures, changing to another membrane type should be an option but not a requirement.  Proposed change (if any):  Please consider alternative controls, e.g. high operating pH and change in addition into: “……and a more harsh chemical sanitisation system ~~must~~ may be considered with respect to current system performance”.  OR  Delete italic text in lines 110-113  Please remove the combination of different methods as this depends on raw water source, system design and system validation (see also comment on lines 76 – 78). |  |
| Lines  114-115 |  | Comment:  Statement “…to test membranes routinely for any potential integrity breaches…” needs to be clarified or changed. RO membranes are not tested using filter integrity test methods applied to product filters or vent filters.  RO membrane integrity tests are not available on the market.  Conductivity monitoring for RO membranes feed water and RO permeate is sufficient for the integrity test. TOC monitoring of the permeate may be also helpful to verify a proper function of the RO.  Proposed change (if any):  Systems should be in place to test membranes routinely for any potential integrity breaches that could lead to a significant contamination event e.g. by in line conductivity monitoring of permeate. |  |
| Lines  114-118 |  | Comment:  The use of double pass RO is only one option (mentioned in the monograph) to increase robustness of the entire WFI production process.  Proposed change (if any):  Either remove lines 116 – 117 or include other techniques, depending on the water quality attribute that should be addressed (and as it is stated in the monograph). |  |
| Line  123 |  | Comment:  “… made from a chlorine-resistant material to withstand periodic sanitisation.”  The focus on chlorine is too stringent and supports only chlorine resistant membranes. The focus should be broadened and include other chemical agents. Chlorine is only one of many options. Thermal methods, i.e. hot water sanitisation, should be added.  Proposed change (if any):  Reword to read: “The MF/UF membranes should be made from a material to withstand the effective sanitisation agents for periodic chemical sanitisation or thermal sanitization (hot water).” |  |
| Lines  124-136 |  | Comment:  The risk mitigation strategy based on TOC measurement should depend on raw water source and system design.  At minimum the TOC should be measured downstream of the final purification step. Additional sampling points should exist after each treatment stage to enable water sampling. But those sampling points relate more to microbiological aspects instead of TOC. Usually TOC does not change in the water treatment plant till the TOC reducing treatment step.  Due to its sensitivity, TOC is not appropriate to measure membrane integrity or UV lamp operation. UV lamp operation and replacement is indicated by measuring the radiation intensity and/or the operating time of the UV lamp.  Proposed change (if any):  Delete lines 130- 133. |  |
| Lines  138 – 142 |  | Comment:  The measures described may be misleading and in case of a microbiological system contamination many countermeasures might be appropriate (including e.g. recirculation of water, discarding water, membrane exchange, sanitisation).  Simple recirculation of water might be an inappropriate corrective action.  This measure is more for continuous system operation to avoid downtimes.  Proposed change:  Include other appropriate countermeasures and clarify context (with respect to continuous operation of the water treatment system). |  |
| Lines  143-144 |  | Comment:  The statement “When on-line TOC systems fail, robust corrective measures should be put in place that will assure the ongoing quality of the water produced” would be more helpful if examples of corrective measures are included.  Please refer to the TOC system downstream of the final purification stage.  Proposed change (if any):  Please add: When on-line TOC systems downstream of the final purification stage fail, robust corrective measures should be put in place that will assure the ongoing quality of the water produced (e.g. at-line measurement with a mobile lab-TOC system, replacement TOC system, sampling for offline TOC measurement). |  |
| Line 151 - 160 |  | Comment:  The application of a risk based approach should be mentioned.  Proposed change (if any):  Please add: The location of on-line conductivity measurements should be based on a risk assessment. |  |
| Lines  164-165 |  | Comment:  “Resistance” is misguiding, e.g. no resistance to disinfectants is yet published. It is scientifically agreed that the resistance to heat for gram-negative bacteria is very low, please refer to A.T. Spinks, et. al., Thermal inactivation of water-borne pathogenic and indicator bacteria at sub-boiling temperatures, Water Research 40, 2006, S. 1326-1332  Proposed change (if any):…procedure, based on the flora of the concerned microorganisms and their physiological capabilities. |  |
| Lines  166-170 |  | Comment:  Regarding “The RO membranes are currently not designed to withstand pressurised steam …”, please remove sentence starting on Line 166.  Further development is highly speculative; see comment line 108-113.  Please do not include discussions / expectations on storage and distribution systems in the scope of this document  The common practice for thermal sanitisation is hot water sanitisation at minimum temperature of 80 °C.    Hot water sanitisation and / or chemical cleaning/sanitisation might not be performed with the same frequency. E.g. Hot water sanitisation is performed regularly (high frequency – e.g. weekly) and chemical cleaning/sanitisation is performed 2-4 times per year.  Proposed change (if any):  Delete lines 166-170. |  |
| Lines  171-174 |  | Comment:  This is an incomprehensive list of suitable sanitising agents. Please label this as a list of examples.  Proposed change (if any):  Please add at least “Sodium hydroxide” as commonly known and potent sanitising agent. |  |
| Lines  176 - 183 |  | Comment:  The use of ozone for sanitisation should be based on a risk assessment that considers process- and material of construction impact as well.  Ozone sanitization is industry standard for distribution systems but not for water treatment plants.  The paragraph will hamper the installation of systems with other materials of construction.  Proposed change (if any):  Please delete sentence to not favour stainless steel as construction material. Stainless steel is only one common and widespread material of construction besides others.  OR  Delete the complete paragraph due to the fact that ozone is not a common method for the sanitisation of water treatment systems.  OR  Include a risk based approach that covers both, process and material of construction aspects. |  |
| Lines  195 - 204 |  | Comment:  Stages of pre-treatment and pre / post RO membrane are usually not subject to sampling during qualification (and routine monitoring).  Please remove the requirements for storage and distribution.  Proposed change (if any): delete lines 201, 202, 204 - 206. |  |
| Lines  218-219 |  | Comment:  The requirement should not be different to distillation systems during routine operation.  Lines 218-219 are contradictory to lines above.  As online devices are operating constantly, there is no concern with respect to physico-chemical parameters (i.e. TOC and conductivity).  Proposed change (if any):  “At minimum one sampling point of the distribution system has to be sampled every day and all sampling points have to be sampled once per week (according to a rotating sampling schedule). The sampling schedule is underlying a risk assessment that finally determines the sampling frequency.  OR  Delete lines 218-219 (Change has to be in alignment with lines 379 – 381). |  |
| Lines  225–226  227-239 |  | Comment:  The requirement “*Use of rapid microbiological methods should be employed as a prerequisite to the control strategy to aid with rapid responses to deterioration of the system.”* is too stringent. While such methods, if correctly set up and validated, may replace the requested microbiological release methods or add value, they are currently not an essential element of designing and maintaining a water system delivering water of the appropriate quality.  Proposed change (if any):  After thorough validation (see also comment for line 390), alternative rapid microbiological methods may be used to replace the requested microbiological release methods. Rapid microbiological methods could also be used as a part of the overall control strategy. They may aid the design of the control strategy enabling rapid responses to deterioration of the system.”  Delete lines 227-239. |  |
| Lines  303-306 |  | Comment:  Proposed change (if any): please insert Cross-reference to PartII/chapter 4. |  |

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| Line 318 - 331 |  | Comment:  Please make the list more specific.  Proposed changes:   * Design   + Feed water system     - design     - quality   + Treatment system design, e.g.     - turbulent flow     - no dead legs     - drainage     - materials of construction and roughness of surfaces (stainless steel, plastics, gaskets and elastomers)     - welding’s     - air filter (incl. integrity)   + Cleaning and sanitation procedures * Water system qualification * Personnel qualification / training * Raw Materials e.g.   + Water supply   + Ion exchange materials   + Cleaning and sanitation materials * Control strategy including in-process controls applied to   + Raw Materials   + Feed water system   + Treatment system * Monitoring systems (qualification / calibration) used in the control strategy * Preventative maintenance to a standard that will not add significant risk from a contamination view point   + Feed water system   + Treatment system   + Premises where the systems are placed   + Other nearby systems that potentially can contaminate the water systems * Utilities e.g.   + Compressed air   + Ventilation in the plant * Robust QMS   + Deviation handling   + Root cause analysis (investigations)   + CAPA |  |
| Lines  352 -353 |  | Comment:  It is essential for debris removal to empty and refill the entire system with fresh water to remove all cell debris (=TOC) after the treatment. This prevents the re-growth of a biofilm.  Proposed change (if any): Appropriate removal of cellular debris should also be considered, as excessive debris can result in increased levels of endotoxin etc. existing within the system, e.g. by emptying and refilling the entire system with fresh water. |  |
| Lines  354-355 |  | Comment:  The statement “*Frequent, rotation of disinfectants & detergents and inclusion of sporicidal agents should be considered as part of a robust strategy*.” is not directly relevant to the management of a water system and needs to be expanded to explain its relevance or deleted.  The sentence is well applicable to cleaning and disinfection procedures in facilities or for equipment. It is not applicable to water distribution and storage systems.  Rotation of disinfectants is not necessary.  Please refer to USP1072 and other publications about this topic.  (USP 1072: The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely to occur at significant levels, as disinfectants are more powerful biocidal agents than antibiotics. In addition, they are normally applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound.  Proposed change (if any): delete  or  refer to comment on lines 164 – 165  or  Change to read: The use of disinfectants & detergents and inclusion of sporicidal agents should be considered as part of a robust strategy. |  |
| Lines  364 -365 |  | Comment:  There seems to be redundancy with lines 171 – 181 and with lines 76 – 78.  Proposed change: Suppress the paragraph. |  |
| Lines  364-365 |  | Comment:  See comment above (line 166-174). Sodium hydroxide is typically used for chemical cleaning of RO for removal of organics followed by H2O2 sanitization.  Proposed change (if any):  Please add Sodium hydroxide. |  |
| Lines  166 – 183  Lines  364 - 371 |  | Comment:  Please make it clearer in the text, which sanitisation methods are recommended for distribution and storage and which are recommended for production systems. As this document refers to the treatment systems it should only reflect the sanitisation methods for this part of the water systems.  Proposed change (if any):  Clarification of the text as outlined above or remove sanitisation methods for distribution systems. |  |
| Line  367 |  | Comment:  Please refer to common practice (hot water sanitisation).  Proposed change (if any): Use of hot water sanitisation should also be considered. |  |
| Line  368-371 |  | Comment:  It is not industry practice to use double edged approach. The success of a sanitisation procedure is based on frequency and time and not necessarily on a combination of two different principles.  Proposed change (if any): Please delete. |  |
| Lines  385 |  | Comment:  “Use of more sensitive endotoxin detection methods should also be taken into account.” It is not clear why these more sensitive tests should be taken into account.  Proposed change (if any):  Please add clarification as to why these more sensitive tests should be taken into account. |  |
| Line  389-391 |  | Comment:  The statement “Taking into account the speed at which organisms can proliferate, the use of rapid microbiological test methods and systems should be employed in order to improve or increase the probability of early detection and allow timely action to be taken.” overstates the capability of rapid microbiological methods used to robustly and consistently monitor water systems.  Proposed change (if any):  “Taking into account the speed at which organisms can proliferate, the use of rapid microbiological test methods and systems should be considered in order to improve or increase the probability of early detection and allow timely action to be taken.” |  |

Please add more rows if needed.