Update: Final version of the EMA Q&A paper on WFI production without distillation

by Fritz Röder

The final version of the Q&A document from the EMA on WFI production using membrane processes was published in August 2017. Significant changes in comparison to the draft from August 2016 should be noted. This article highlights:

- What has been changed
- Which questions remain unanswered
- Where things will go from here

The revised monograph for water for injection (WFI) from the European Pharmacopoeia dated April 2017 provides a legal basis for the production of WFI using membrane processes. However, what this might look like in practice is still not universally resolved. In comparison with the draft document for the Q&A paper, however, numerous aspects have by now become clear or no longer appear in the final version.

We have already reported extensively on the draft of the guideline in LOGFILE 36/2016. As before, the Q&A document comprises two parts: *The production of WFI using membrane technology* and *biofilm control strategies*. From the outline, it is already possible to discern that the focus is clearly on the consideration of microbiological risks. This is also in line with the author's opinion. Owing to the lack of vaporisation of the water, the microbiological risks in particular should be assessed differently. This is one of the main reasons why the use of alternative high-speed methods for the microbial count and endotoxin detection is recommended multiple times (with reference to EP section 5.1.6).

Part one: Production of WFI by non-distillation methods

Overall, the first part of the document focuses very strongly on reverse osmosis, which represents the barrier to germs. Additional control mechanisms such as measurement of the total organic carbon (TOC) at multiple points during preparation or membrane autopsy ("destructive analysis") are mentioned. The information about the autopsy is new in the final document, as is the establishment of maximum hold times for reverse osmosis membranes.

In monitoring, very frequent sampling is still recommended ("Daily sampling of the system should be employed for all user points utilised on the day..."). Here, a precise risk assessment helps to evaluate the criticality of the outlets. However, how the samplers should know at the beginning of the day which outlets should be sampled on that day remains unclear.

The use of (expensive) online measurement technology has already been the subject of intense discussion within the industry: online microbial count measurement devices have not been on the

market for long. From a measuring technology point of view, the common types for water monitoring are particle counters with an additional device which detects the ATP luminescence. The device is thus able to differentiate between living and non-living particles. However, pharmaceutical companies' initial experiences have shown that these devices do not yet measure perfectly. Successful validation of this method is questionable. In addition, conventional sampling and incubation with a suitable growth medium would give microbial numbers different to those obtained using an online microbial count measurement device, which detects all organisms. This means that demonstrating the comparability of the two methods would be difficult. Summary: since the water monographs require a microbial count according to the classic method, this should also be used for release. Any online measurement technology can therefore currently only be used as an additional in-process control. It is to be hoped that the new measuring devices are further developed in order to be better used in the future.

The new high-speed methods for endotoxin detection also show difficulties in comparability with the traditional LAL test. In addition, incubation over several days is not required for the LAL test as it is for the microbial count. Initial measurement values are therefore relatively quickly available, even for the traditional endotoxin test.

Part two: Biofilms and control strategies

The second part of the document deals with the topic of "biofilms" and controlling them. A flexible sanitisation concept which allows for the use of multiple procedures is recommended for this purpose. This includes hot water sanitisation and chemical procedures using ozone, hydrogen peroxide, sodium hydroxide or other chemicals. The appropriate sanitisation method should be used, depending on the type of a possible infestation. However, this also requires the system components to be resistant to the procedure.

But the biofilm control strategy not only includes the sanitisation, it should also be applied holistically. According to the document, the following areas should be involved:

- Design
- Qualification
- Training
- Raw materials (feed water, materials for the components)
- In-process controls
- Monitoring
- Preventive maintenance
- Supply media
- Quality management system (deviation management, root cause analysis, CAPA)

The document has already been evaluated and discussed by experts in the industry. In principle, the fact that the EMA has published such a document should be welcomed. Unlike the US Pharmacopoeia, there is scarcely any guidance in the European regulations for dealing with water systems (e.g. the procedure for performance qualification), and this new document addresses these issues well. However, not all questions have so far been answered, for which reason the equipment constructors' and pharmaceutical manufacturers' experts now want to position themselves. In addition, reference is made to the existing 15 years of experience with systems for the production of "highly purified water", which have to comply with the same limits as for WFI. The now revised risks are considered, overall, by industry representatives to be a little more moderate than appears to be the case for the governmental representatives.

Conclusion and outlook

In a nutshell, it can be said that some, but not all, of the doubts concerning future WFI production have been cleared up with the EMA document. In order to fill this gap, the experts in the industry are asked to implement the requirements from the guideline in practice. Initial experiences with membrane systems are sure to contribute valuable insights on the topic as well.

Source:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/08/WC500232814.pdf

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Further reading:

The New USP <1231>: Water for Pharmaceutical Purposes

The pdf download highlights the following aspects of the new USP <1231>:

- Short overview – What is USP <1231> and what is new?
- Detailed overview with explanations and important notes
- Source water considerations
- Monographs of water qualities
- Validation and qualification of water systems
- Design and operation of water systems
- Sampling
- Chemical evaluations
- Microbial evaluations
- Alert and action levels and specifications

