

## **EXPERT WORKSHOP**

# **WATER FOR INJECTIONS – POTENTIAL USE OF MEMBRANE SYSTEMS FOR THE PRODUCTION**

## **SUMMARY REPORT**

**Strasbourg (France)**

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**European Directorate for the Quality of Medicines & Healthcare (EDQM)**

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## 1. INTRODUCTION

On 24/03/2011 the European Directorate for the Quality of Medicines and HealthCare organized an expert workshop bringing together representatives from European competent authorities, Pharmaceutical companies and relevant stakeholders to discuss the use of membrane technologies for the production of water for pharmaceutical use, especially if the quality of the water produced by such techniques could be considered equivalent to Water for Injections (WFI) which, according to the European Pharmacopoeia (Ph. Eur.), is produced by distillation techniques only.

The workshop aimed at providing the Ph. Eur. Commission with information regarding the possible need to initiate a revision of the concerned monograph (*Ph. Eur. monograph 0169: Water for injections*) and the implication for other related monographs and general chapters.

## 2. INTERNATIONAL REGULATORY BACKGROUND, REGULATORS' EXPERIENCE AND CONCERNS

The respective pharmacopoeias of the ICH regions require the production of WFI to be performed by:

- Europe: Distillation only
- USA: Distillation or suitably validated method.
- Japan: Distillation or membrane techniques. For membrane techniques specific requirements for the design and operation of the system have to be considered.

Further to recent discussions within the different European scientific committees and considering the developments over the last decade in membrane technologies and recent issues in WFI production, the Ph. Eur. Commission had decided to re-evaluate the pertinence of restricting the production of WFI to distillation only.

### **Concerns from European regulators**

The concerns were mainly related to the microbiological quality of the water produced by the membrane systems considering systems where reverse osmosis (RO) membrane was the major element. The progressive development of biofilms in such systems and the potential micro-organisms and/or by-products release were considered as major issues.

### **International Experience**

Between 2004 and 2010, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.) had issued several surveys to identify current practices in place in companies for water generation with an emphasis on membrane systems. All the systems where data had been reported (regardless of the body organizing the survey) were (either or/and):

- Coupling at least three individual purification units;
- Including initial water pre-treatment (filtering/softening)
- Coupling units based on different principles (e.g. RO, ultrafiltration, electro-deionisation...);
- Specifically designed to minimize biofilm formation (e.g. avoid deadlegs, allow full drainage ...);
- Operated with specific maintenance/sanitization scheme
- Coupling continuous in-process controls and fixed interval sampling

The data gathered were essentially similar between the different regions regarding the values routinely achieved for membrane systems for TOC, bacterial endotoxins, conductivity and bioburden. In addition information had been obtained regarding the heterogeneity in the design of these systems. Similarly, additional information regarding various sanitization regimens applied to these systems had also been identified.

The data collected during these three surveys had confirmed that the quality of the water produced by properly operated and designed membrane systems was meeting current WFI specifications. These data also provided updated information regarding the actual values achieved by these systems for the parameters currently monitored. It was noted in particular that the specifications currently set in the WFI monograph were, for specific parameters, far above actual values reached, thereby questioning the relevance of such high specifications considering the improved performances of these systems.

### **3. MODERN TECHNOLOGICAL CAPABILITIES AND EXPERIENCE FROM PHARMACEUTICAL COMPANIES**

#### ***Capacity and performance of modern distillation systems and modern membrane systems***

For modern membrane systems, RO was no longer used as final stage in water generation due to known weaknesses. Other modules such as UF were preferred. Each treatment steps in a membrane system train was based on different working principles and the quality of the water was built with each step. The sanitization operations carried out and their frequency were highlighted as critical points to ensure that the system was kept under control. Information was provided regarding membrane systems used in other industries (e.g. semiconductor/electronic), the specifications applied for ultrapure water required by these industries and the design of the systems used. For certain parameters the requirements were equivalent to specifications 1000 times stricter than those used for WFI.

The advances in the technology and materials used for membrane production were also underlined as a major factor of improvement over the last decade especially regarding the performance and integrity of the concerned membranes.

#### ***Experience from pharmaceutical companies***

Representatives from pharmaceutical companies having provided significant amount of data to the survey were given the opportunity to present the membrane system currently in operation in their company for production of highly purified water. These presentations were also the opportunity for representatives from industry to underline issues that were faced during installation/operation of their system, areas where additional guidance from authority would be helpful and additional investigations performed when issues occurred.

### **4. GENERAL DISCUSSION**

#### ***Should the Ph. Eur. Commission recommend to open the discussion for a revision of the WFI monograph to consider alternative systems to distillation for the production of WFI?***

The participants agreed that sufficient knowledge and experience had been acquired since this topic was first raised in the late 90's and that a discussion on alternatives to distillation in the framework of the Ph. Eur. would be beneficial. However, such an evolution would be likely to induce significant changes in the monograph. Several items to be considered were further discussed.

#### ***Presence of micro-organisms in water systems***

Regarding membrane systems, presence of micro-organisms in the production systems was acknowledged by the participants, especially for those systems operated at ambient temperature. The purpose of having successive units in these systems was to stepwise reduce the level of contaminants depending on the characteristics of these materials.

From the data shown in various case studies, the different contamination events of the entire system (production+distribution) had been detected and the system was back under control after appropriate maintenance and/or sanitization had been carried out.

Monitoring of the flora in the system was also considered as critical information to allow adaptation of the sanitization procedure based on known resistance of the concerned micro-organisms.

### ***Micro-organisms control and monitoring of membrane systems***

In theory, the most appropriate way to ensure that micro-organisms were under control would be to ensure that none of them would be allowed to penetrate the system and that it was operated and maintained under strict conditions in line with GMPs. Although strict application of GMPs was considered to be the standard practice in the pharmaceutical industry, water systems would never be fully closed systems due to their primary function. Feeding of raw water, maintenance of the equipment and distribution of the water produced through points of use would be acting as potential entries for micro-organisms into the system.

Critical parameters highlighted for micro-organisms control:

- Adherent biofilm to inner walls of production/distribution system:
  - o Normal state of bacterial colonies
  - o Be influence by the design of the system (roughness, deadlegs, flow rate,...)
  - o Oligotrophic environment to diminish increase rate of biofilm
  - o Thermophilic micro-organisms and established biofilm less sensitive to heat
- Feeding water quality:
  - o Variability of microbiological flora of feeding water
  - o Seasonal feeding water quality (especially if surface water is used)
  - o Might impact site selection and system design.
- Evolution in membrane technologies allowing improved membrane resistance to high temperature (above 120°C ), pressure and harsh environment (caustic soda)
- Sanitization strategies have to consider multiple approaches to optimize micro-organisms removal (heat+chemical) and not rely on a single principle (e.g. hot water at 80°C).
- Adapt sanitization strategies based on the knowledge of the potential contaminants
- Close monitoring of membranes aging to avoid breakdown by on-line integrity testing.

Regarding monitoring of micro-organisms, tests were performed off-line and on liquid samples.

Such practice was in line with regulatory requirements and adapted to detect a massive contamination. However, its appropriateness for monitoring the system on a continuous rapid basis was questioned considering the nature of biofilms and the fact that release of micro-organisms and other by-products from the biofilm would not be linear. Modern microbiological techniques (Chemscan, ultrafluorescence, flow cytometry) were discussed and were considered as potential powerful tools to:

- Either reduce the time for delivering the results, allowing to trigger preventive/curative measures more rapidly.
- Improve sensitivity for micro-organisms detection
- Or be used as on-line monitoring systems (provided their integration in the water system was technically achievable).

The possibilities to obtain representative surface samples were discussed. However, the collection of these samples was unlikely to be manageable in an industrial scale production system. Nevertheless, systems allowing collection of surface samples (e.g. Robbins device) would present a significant interest at laboratory level to identify the microbiological flora susceptible to penetrate the production system.

Therefore, current practices regarding liquid samples would need to be continued, also the timing and location of sampling could be correlated to triggers (e.g: fluctuation of a physico-chemical parameter) from on-line measurements located through the water system.

***WFI monograph and adequateness of current specifications when considering membrane systems.***

When the specifications of the Ph.Eur. WFI monograph were established, only the distillation technique and the potential contaminants likely to be associated with this technique had been considered. The current specifications of the WFI monograph were not considered appropriate with respect to the potential contaminants likely to be present when using membrane systems for the production of water.

Nevertheless, by-products or remains from micro-organisms would be of organic nature and would likely impact the parameters currently monitored in the monograph. Should such materials be released in the system it was considered that TOC and conductivity would be impacted.

Therefore, the adjunction of requirements regarding stability of values measured on-line for TOC and conductivity might provide information regarding potential presence of micro-organisms in the system or release of by-products.

A significant reduction of the TOC specification would be in line with actual data presented and also provide further control by reducing nutrients availability.

Regarding bioburden, the possibility to reduce the current level should be considered. Amendments regarding the detection of micro-organisms using rapid microbiological methods or modified culture media adapted to bacteria likely to be present in the system, depending on feedwater and environment flora specific for the location, could be considered as well.

Finally, additional methods (for example Monocyte Activation Test, for compounds susceptible to elicit immune response in human or other suitable tests) could be integrated for the detection of by-products biologically active released by micro-organisms in addition to the currently recommended bacterial endotoxins test, that is focused on endotoxins from Gram negative bacteria.

## **5. CONCLUSIONS**

The quality of the discussions and data provided by speakers was very much appreciated. In contrast to the workshop organized in 1999, the representatives from regulatory authorities considered that sufficient reasons had been provided for the European Pharmacopoeia Commission to recommend initiating discussions regarding potential use of membrane systems for the production of Water for Injections. However, such discussions would have to consider the points highlighted during the workshop regarding a revision of the current specifications and the introduction of additional methods and requirement to deal with the contaminants likely to be present in such systems and ensure an acceptable safety level of the material produced. Finally, since the topic was considered as having a major impact on regulatory authorities and pharmaceutical companies, the participants from the workshop strongly recommended that discussions be held in a multidisciplinary forum involving the various stakeholders, to ensure that all aspects related to this topic are adequately covered.