Reverse osmosis in Ph. Eur. monograph *Water for injections (0169)*

The purpose of this document is to provide background information on the revised version of the monograph Water for injections (0169), published in Supplement 9.1 of the European Pharmacopoeia (Ph. Eur.).

There have been ongoing discussions for many years as to whether there is a need to include non-distillation techniques as a method for production of Water for injections (WFI). In 1999 a major international symposium was held in response to requests from national pharmacopoeia authorities to discuss whether evidence was available to support the introduction of reverse osmosis (RO) as a production method for WFI. At that time, it was agreed that the available evidence for such a change was lacking, but in view of the comments the Ph. Eur. Commission decided to introduce a monograph on highly purified water (HPW) in the Ph. Eur., *Water, highly purified (1927)*, which was implemented in 2002. This HPW has the same specifications as WFI and may be produced by RO and ultra-filtration techniques (UF).

In 2010, discussions on the use of techniques considered as equivalent to distillation were re-opened. After further requests from users of WFI, the EDQM began a process to investigate whether it was viable to include non-distillation technologies for the production of WFI. This included issuing a survey in March 2010 to gather available data for the use of non-distillation technologies for the production of WFI and to determine whether the issues raised (range of separation, validation of devices and microbiological control) in the EMA *Reflection Paper on Water for Injection Prepared by Reverse Osmosis* [EMEA/CHMP/CVMP/QWP/28271/2008] could be addressed. The feedback from this survey indicated that companies supplying data on non-distillation/membrane-based technologies were consistently able to meet the current specifications detailed in the WFI monograph. However, it was noted that, rather than just employing RO alone, these non-distillation technologies for the production of water included additional production modules such as UF and the treatment of the water with ultraviolet light or ozone. Evidence was also supplied that showed that the quality of feed water and continuous use of the non-distillation systems, as well as the design, validation, performance monitoring and sanitisation of the system were crucial to the consistent production of water of equivalent quality to WFI as described in Ph. Eur. monograph 0169.

Since the time of these discussions and the subsequent decisions, distillation has been regarded as the benchmark standard for WFI by European Regulatory Authorities.

In March 2011, as a follow-up to the survey, the EDQM organised an expert workshop bringing together representatives from European competent authorities, pharmaceutical companies and other relevant stakeholders to discuss the use of membrane-based technologies for the production of water for pharmaceutical use. The workshop was intended to provide the Ph. Eur. Commission with information bearing on the possible need to revise the WFI monograph (0169) and the potential impact on related

monographs and general chapters. The main concerns raised during the workshop were related to the microbiological quality of water produced by membrane systems. It was argued that the potential for progressive development of biofilms and the potential for fouling of the water by micro-organisms and/or by-products remained major issues in such systems.

It was noted that, for modern membrane systems, RO was no longer used as the final stage in water production and that other production modules, such as UF, were preferred. Each treatment step in the production of water by non-distillation systems was based on different working principles and the quality of the final water was enhanced with each step in the production. It was emphasised that the monitoring and sanitisation of such systems and the frequency with which these operations were performed were critical to keeping the system under control.

It was also noted that membrane water-production systems were likely to be suited to consistent and reliable production of large volumes of high quality water. Membrane technology systems used to produce very high quality water in the micro-electronics industry have a capacity of about 300 m^3/h and run constantly for 365 days per year with water quality specifications more stringent than those of the pharmaceutical industry (see Annex 1). It should be possible to apply the experience from the non-pharmaceutical industry to the pharmaceutical manufacturing environment.

Owing to the quality of the discussions and the data provided by speakers at this workshop, in contrast to the workshop organised in 1999, the regulatory authorities' representatives considered that sufficient reasons had been provided for the Ph. Eur. Commission to recommend initiating discussions on the potential use of non-distillation technologies for the production of WFI. These discussions were also to consider the introduction of additional methods and requirements to deal with contaminants potentially present in non-distillation water-production systems and to ensure acceptable water quality.

The Ph. Eur. experts reviewed all the evidence and scientific data collected. The specifications for HPW and WFI set out in the Ph. Eur. are identical and are detailed in Table 1. The data provided by companies using non-distillation technologies to produce HPW (Table 2), when compared with the specifications for WFI, show that water of a quality equivalent to WFI is being produced by these systems.

Although ongoing concerns were expressed at the March 2011 workshop that micro-organisms could be present in any non-distillation water-production system, this was deemed not necessarily to be an issue for the production of WFI provided that the micro-organisms are suitably controlled and that the final quality of water is appropriate. Furthermore, such concerns are equally applicable to the distribution pipework for distillation systems. It is recognised that the quality of feed water is important and this is reflected in current designs of non-distillation water-production systems. Most systems use feed water of consistent potable quality that is not susceptible to seasonal variations (e.g. avoidance of surface-water use). In addition, the systems are designed to avoid the adherence of micro-organisms in biofilms by minimising the roughness of the inner walls, dead legs or areas with inappropriate flow. Because the growth of any biofilm is largely dependent upon the amount of nutrients (organic compounds) available within the system, maintenance and continuous monitoring of an oligotrophic environment (low total

organic carbon (TOC)) within the water system considerably slows down biofilm growth; however, it neither stops nor destroys it. The use of membranes that are able to cope with high temperatures (more than 120 °C), high pressure and harsh environments during the sanitisation process(es) is a major improvement that has been introduced over recent years. This has allowed the introduction of hot water (usually at 80 °C), clean steam (above 120 °C) and chemical sanitisation or constant operation of membrane systems at elevated temperatures (i.e. 80 °C); the heat treatment of membranes can, however, affect their lifespan. Some thermophilic micro-organisms are not destroyed by heat alone so systems using additional modes of action for sanitisation are deemed necessary and the use of detergents (acidic or alkaline) is considered to complement efficiently the action of hot water.

Continuous measurement of physico-chemical parameters such as TOC, conductivity, temperature and pressure enables alerts to be triggered whenever values reach pre-defined limits so that action can be taken. In addition, based on increased knowledge of membrane ageing and lifespan, a safety margin can be determined for replacement of membranes before they fail. Rapid microbial enumeration and identification techniques are increasingly being used and are considered as potentially powerful tools that can reduce the time needed to obtain results and to take preventive/curative measures.

The EMA GMP/GDP Inspectors Working Group (GMDP IWG) and the joint CHMP/CVMP Quality Working Party (QWP) have both been consulted on the proposed change. A general revision of Annex 1 ‘Manufacture of sterile medicinal products’ to the EU Good Manufacturing Practice (GMP) guidelines is ongoing and will include new guidance on production methods for WFI. A Q & A document on WFI via RO and biofilm control strategies is being prepared by the GMDP IWG; this document will be available when the revised monograph comes into force.

The Ph. Eur. Commission has undertaken the revision of the WFI monograph (0169) to include non-distillation technologies for the production of WFI. This revision is justified by the following:

- the consistent performance of non-distillation systems;
- RO no longer being used as a final stage of production;
- a recognition that all water-production systems are a series of interdependent unit processes which rely on the optimum functioning of each process to ensure that water of an acceptable quality is produced; the water quality has to be built up stepwise by successive treatments;
- advances in the technology and materials used for membrane production;
- 20 years of experience in non-distillation technologies;
- system design improvements to avoid dead legs and allow drainage and sanitisation;
- advances in process controls and in-line monitoring of specification parameters;
- improvements in rapid microbial methods reducing the time needed to obtain results;
- evidence that systems are constantly meeting WFI specifications.

The Ph. Eur. defines the quality of WFI, and acknowledges that the design, failure mode and maintenance of any water-production system plays an important role in ensuring that

appropriate water quality is established and maintained. However, it is the responsibility of the manufacturer to demonstrate compliance with good manufacturing practices, requirements for system design, operation and maintenance, including validation and monitoring as laid down in the European Union. Nevertheless, the design and maintenance of systems will also have to be considered by appropriate stakeholders and incorporated into existing guidance documents. Quality assurance and monitoring should extend to storage and distribution processes for WFI to ensure quality is maintained at the point of use.

Table 1 – *Current Ph. Eur. specifications for highly purified water (HPW), water for injections (WFI) and sterilised water for injections (SWFI)*

	HPW	WFI	SWFI
PRODUCTION			
Microbial monitoring	Action level: 10 CFU / 100 mL	Action level: 10 CFU / 100 mL	N.A.
Total organic carbon (TOC)	0.5 mg/mL = 500 ppb	0.5 mg/mL = 500 ppb	N.A.
Conductivity	0.6-4.7 µS·cm^{-1}	0.6-4.7 µS·cm^{-1}	N.A.
Heavy metals	N.A.	N.A.	N.A
TESTS			
Conductivity	N.A.	N.A.	2 µS·cm^{-1} (containers ≤ 10mL) 5 µS·cm^{-1} (containers > 10mL)
Nitrates	0.2 ppm	0.2 ppm	0.2 ppm
Aluminium	10 ppb (dialysis)	10 ppb (dialysis)	10 ppb (dialysis)
Heavy metals	N.A.	N.A.	N.A.
Bacterial endotoxins	0.25 IU/mL	0.25 IU/mL	0.25 IU/mL
Acidity or alkalinity	N.A.	N.A.	Pass test
Oxidisable substances	N.A.	N.A.	Pass test
Chlorides	N.A.	N.A.	Pass test
Sulfates	N.A.	N.A.	Pass test
Ammonium	N.A.	N.A.	0.6 ppm (containers < 50mL) 0.2 ppm (containers ≥ 50mL)
Ca and Mg	N.A.	N.A.	Pass test
Residue on evaporation	N.A.	N.A.	0.004 per cent (containers ≤ 10mL) 0.003 per cent (containers > 10mL)
Total aerobic microbial count (TAMC)	N.A.	N.A.	N.A.
Particulate contamination	N.A.	N.A.	Pass test
Sterility	N.A.	N.A.	Sterile

Table 2 – *Data provided by pharmaceutical companies on the performance of non-distillation technologies for the production of HPW and purified water (PW)*

No.	Pharmaceutical company products	Type of system used	Grade of water produced	Parameters monitored during production	Estimated performance of the water system
1	Human	Feed = PW: degasifier + water softener Peak load system: 0.2 µm filter + UF (Cut-off: 10 000 Daltons) Part load system: 0.2 µm filter + UF (Cut-off: 6000 Daltons)	HPW	Bioburden	1 CFU / 10 mL
				TOC	500 ppb
				Conductivity	1.3 µS.cm^{-1}
				Endotoxins	0.25 EU/mL
				Physico-chemical parameters	Not communicated
2	Human	Filtration + water softener + RO + EDI + UF	HPW	Bioburden	1 CFU / 10 mL
				TOC	< 500 ppb
				Conductivity	< 2.1 µS.cm^{-1}
				Endotoxins	< 0.25 EU/mL
				Physico-chemical parameters	Not communicated
3	Human	Water softener + RO + EDI + membrane degasification + UF	HPW	Bioburden	10 CFU / 100 mL
				TOC	500 ppb
				Conductivity	0.3 µS.cm^{-1}
				Endotoxins	0.15 EU/mL
				Physico-chemical parameters	Not communicated
4	Veterinary	Water softener + microfiltration + 3 RO modules in cascade	WFI (claimed)	Bioburden	10 CFU / 100 mL
				TOC	350 ppb
				Conductivity	2.5 µS.cm^{-1}
				Endotoxins	0.25 EU/mL
				Physico-chemical parameters	Not communicated
5	Veterinary	Double-pass RO	PW	TAMC	1 CFU / 10 mL
				TOC	25 ppb
				Endotoxins	< 0.025 EU/mL
				Conductivity	Not communicated
				Physico-chemical parameters	Not communicated

Annex 1

The International Technology Roadmap for Semiconductors (collaborative entity sponsored by the 5 leading chip manufacturing regions in the world) details water quality achieved for semi-conductor manufacture as below[1]:

- Conductivity at 25 °C: max 0.05 µS.cm^{-1} (fundamental conductivity of ultrapure water);
- TOC: < 1 ppb.mL^{-1};
- Bacteria: < 1 CFU.L^{-1} (1 L is the minimal volume to be analysed).

Other parameters of interest:

- Metals: < 1.0 ppt or < 10 ppt (parts per trillion, depending if critical or less-critical metal);
- Ions: < 50 ppt (except phosphate, which is limited to 20 ppt due to its size);
- Particles: < 4000 particles/L at 40 nm (40 nm is recommended for DRAM (memory chip) manufacturing; Ph. Eur. (*2.9.19*) calls for < 25 particles/mL at 25 µm).

1 Data extracted from *ITRS 2010 Update – Technology Requirements for Water Environmental Contamination Control* (for background information on ITRS see www.itrs.net).