Reverse Osmosis in Ph. Eur. Monograph for Water for Injections: an Overview

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Points to be addressed

- Introduction to the Ph. Eur.
- History Water for Injections (WFI)
- Ph. Eur. actions
  - Data gathering: use of non-distillation technologies for production of water for pharmaceutical use
  - Reflection Paper: Reverse Osmosis and WFI
- Revision of WFI monograph: update on current status
Introduction

The purpose of the European Pharmacopoeia is to promote public health by the provision of recognised common standards for the quality of medicines and their components. Such standards are to be appropriate as a basis for the safe use of medicines by patients.

Place of the Ph. Eur. within EU regulatory network

- Lays down common, compulsory quality standards for all medicinal products in Europe.
- Mandatory on the same date in 37 states (CoE) and the EU (European Union Directives 2001/82/EC, 2001/83/EC, and 2003/63/EC, as amended, on medicines for human and veterinary use).
- The Ph. Eur. is legally binding. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market.
- Needs to keep pace with:
  - regulatory needs of licensing, control and inspection authorities in the public health area
  - technological and scientific advances, and with industrial constraints.
Ph. Eur. – General organisation

- Introduction
- General notices
- General chapters
- General monographs
- Individual monographs

- apply to all monographs and other texts of the Ph. Eur.
- instructions to understand texts, conventional expressions
- essential reading before starting to use monographs

Ph. Eur. texts

- classes of substances, dosage forms
  - Substances for pharmaceutical use (2034)

- Quality aspects that cannot be dealt with in each individual monograph
- Quality aspects that are common to a class of products
- Classes defined by different criteria: production method, origin, risk factors
- General monographs apply to all substances and preparations within the scope of the DEFINITION section of the general monograph, except where a preamble limits its application
Ph. Eur. texts (cont'd)

- based on approved specification(s) backed up by batch data
- specifications for drug substance or finished products
- analytical procedures and acceptance criteria to demonstrate that the substance meets required quality standards

**DEFINITION**: official definition, chemical structure

**PRODUCTION**: instructions for manufacturers

**IDENTIFICATION**: specific physical and/or chemical tests and reactions

**TESTS**: principally directed at limiting impurities; certain tests may apply to special grades (dialysis solutions, etc.) or may have a special limit for a particular use

**ASSAY**: physico-chemical assay methods, bio/immuno-assays, unless tests performed are sufficient to establish the quality of the substance, usually a non-active ingredient (e.g. water)

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Ph. Eur. texts (cont’d)

**standard analytical methods**

- **General requirements for equipment**
  - Total organic carbon (2.2.44)
  - Bacterial endotoxins (2.6.14)
  - Particulate contamination: sub-visible particles (2.9.19)
  - Sterility (2.6.1)
  - Alternative methods for control of microbiological quality (5.1.6)

- Editorial convenience: avoid repeating standard methods in each monograph
- Provide standard methods that can be used where there is no monograph
- Give general requirements for equipment, equipment verification
- Not mandatory per se
- When referred to in a monograph, they become part of the standard
**Ph. Eur. reference standards**

- Established specifically for use in monographs or general chapters of the Ph. Eur., as prescribed in the methods given
- **Chemical Reference Standards (CRSs) and Biological Reference Preparations (BRPs)**

**PRODUCTION section in a Ph. Eur. monograph**

**General Notices:** “Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute **mandatory requirements for manufacturers**, unless otherwise stated. They may relate, for example, to source materials; to the manufacturing process itself and its validation and control; to in-process testing; or to testing that is to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The **competent authority** may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.”
Ph. Eur. WAT Monographs (1/3)

<table>
<thead>
<tr>
<th>Water, purified</th>
<th>Water for Injections</th>
<th>Water, highly purified</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ph. Eur. 0008) PW</td>
<td>(Ph. Eur. 0169) WFI</td>
<td>(Ph. Eur. 1927) HPW</td>
</tr>
</tbody>
</table>

Other:

- Water for diluting concentrated haemodialysis solutions (Ph. Eur. 1167)
- Water ($^{18}$O) injection (Ph. Eur. 1582)
- Tritiated ($^{3}$H) water for injection (Ph. Eur. 0112)

Ph. Eur. WAT Monographs (2/3)

**DEFINITION**

- for preparation of medicines other than those that are required to be both sterile and apyrogenic, unless otherwise justified and authorised
- for preparation of medicines for parenteral administration (bulk WFI) and for dissolving or diluting substances / preparations for parenteral administration (SWFI)
- intended for use where water of high biological quality is needed, except where WFI is required
Ph. Eur. WAT Monographs (3/3)

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<th>Water for Injections (Ph. Eur. 0169) WFI</th>
<th>Water, highly purified (Ph. Eur. 1927) HPW</th>
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**PRODUCTION**

- distillation
- ion exchange
- reverse osmosis
- any other suitable method

- distillation only

- double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration and deionisation

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Points to be addressed

- Introduction to the Ph. Eur.
- History Water for Injections (WFI)
- Ph. Eur. actions
  - **Data gathering**: use of non-distillation technologies for production of water for pharmaceutical use
  - **Reflection Paper**: Reverse Osmosis and WFI
- Revision of WFI monograph: update on current status
History Water for Injections (WFI) (1/3)

**1st Publication WFI**
Distillation only

- **1973**

**Ph. Eur. 2nd Edition, 5th Add. – WFI**
Revision: editorial changes (bulk WFI/sterilised WFI)
Distillation only

- **1983**

**1969**

**Ph. Eur. 1st Edition**
Purified Water
physico-chemical tests

**1997**

- **Ph. Eur. 3rd Edition – WFI**
Revision: replacement of in vivo Pyrogens test by LAL (sterile WFI)

- **Distillation only**

**First discussions on RO (double pass):**
- limited experience
- membranes robustness, microbiological control
- potential impurities – not detectable by standard methods
- no data available from systems using membrane technique for producing WFI

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History Water for Injections (WFI) (2/3)

**Revision initiated:**
further guidance to allow closer monitoring of the production

- **1999**

**Ph. Eur. 3rd Edition (Suppl.)**
Revision: Production section
(Bioburden, TOC, Conductivity)

- **2000**

**Renewed discussions on RO**
EDQM International Symposium: need for data & guidance

- **2002**

**Ph. Eur. 4th Edition**
HPW – new monograph
WFI – no modification

**Adoption by CHMP/CVMP of**
Note for Guidance on Quality of Water for Pharmaceutical Use

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History Water for Injections (WFI) (3/3)

- Ph. Eur. monographs on WAT with clear specifications
- EMA Guidance for use of different water grades

2009 – 135th Session of the Ph. Eur. Commission: Ph. Eur. requested to take the lead

Regulatory event:
RO used for producing WFI
EMEA/CVMP/2934/2009

Reflection paper on WFI prepared by reverse osmosis
EMEA/CHMP/CVMP/QWP/28271/2008
Concerns from regulators – Biofilm & microbiological safety

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Ph. Eur. Actions: Phase 1

Objective: GATHER DATA for use of non-distillation technologies for producing water of WFI quality

- HOW? A survey
- Key elements:
  - Participation of a maximum number of companies
  - Sharing of information and open discussion
- Format: questions (supportive data)
  - Range of separation for RO
  - Validation of production system
  - Maintenance of production system
  - Biofilm formation
  - Membrane efficiency
  - Additional tests

OUTCOME:
- data focused on: bioburden, TOC, conductivity and endotoxins
- no data for other physico-chemical parameters

Ph. Eur. Actions: Phase 1/Assessment

- In favour (statements from companies):
  - RO not sufficient – part of purification pathway
  - Coupling additional purification modules
  - Additional treatments: UV light or ozone
  - System design to minimize biofilm formation (e.g. avoid deadlegs, allow full drainage)
  - Regular, specific maintenance/sanitisation needed
  - Validation is achievable
  - Use Purified Water as feed water

- Systems used - large diversity:
  - Degasifier + Water softener + microfiltration + UF
  - Filtration + Water softener + RO + EDI + UF
  - Water softener + RO + EDI + membrane degasification + UF
  - Water softener + microfiltration + (×3)RO
  - Double pass RO
Ph. Eur. Actions: Phase 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated performance of water system</th>
<th>Ph. Eur. monograph limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioburden</td>
<td>10 CFU / 100 mL</td>
<td>10 CFU / 100 mL (action level)</td>
</tr>
<tr>
<td>TOC</td>
<td>25 to 350 ppb</td>
<td>0.5 mg/L (= 500 ppb)</td>
</tr>
<tr>
<td>Conductivity</td>
<td>0.3 to 2.5 µS.cm⁻¹</td>
<td>0.6 to 4.7 µS.cm⁻¹</td>
</tr>
<tr>
<td>Endotoxins</td>
<td>&lt; 0.25 EU/mL</td>
<td>0.25 EU/mL</td>
</tr>
</tbody>
</table>

**RO + additional purification modules:** whatever the design of the system reported, all produce a water meeting current specifications established for WFI

EXPERIENCE FROM PHARMACEUTICAL COMPANIES:

Microorganisms control – critical parameters

- Adherent **biofilm** to inner walls of production/distribution system:
  - system design (roughness, deadlegs, flow rate), oligothropic environment, evolution in membrane technologies
- Feeding water quality (avoidance of surface-water use)
- Evolution in membrane technologies (**improved membrane resistance** to high temperature, pressure and harsh environment)
- Sanitisation strategies to consider multiple approaches (heat + chemical)
- Close monitoring of membranes aging

**OBJECTIVE:**

- Assess whether sufficient data to re-open debate on **introducing non-distilation systems** for WFI production.
- Possible need to initiate a revision of WFI monograph
- Discussion platform for regulators and companies.
- Implication for other related monographs and general chapters.
Ph. Eur. Actions: Phase 2 (cont’d)

Position of the Ph. Eur. Commission:

✓ Progress in the field of pharmaceutical water production was acknowledged and has to be considered.
✓ "...Mandate to the Ph. Eur. Water Working Party to review the production section of the Water for Injections monograph (0169) to consider the inclusion of currently available technologies and evaluate whether additional online monitoring is needed.”


Further discussions to be held in a multidisciplinary forum involving various stakeholders, to ensure that all aspects related are adequately covered.

Ph. Eur. Actions: Phase 3

Further considerations within the WAT WP

- WFI monograph (0169):
  - Can non-distillation techniques be considered safe enough?
    - Current parameters: adapted to non-distillation techniques?
    - Change/Update limits for existing parameters?
    - Add new parameters?
    - Include new control methods?
    - Modify/Update existing control methods?

- Impact on other water monographs
  - Ph. Eur. 0008 – Purified water
  - Ph. Eur. 1927 – Highly purified water
Reflection Paper on WFI (1/2)

The production of water for injections (WFI) is described in the European Pharmacopoeia (Ph. Eur.) monograph Water for Injections (0169). In this monograph the method of production of WFI is limited to distillation only. This is currently distinct from the production methods described in the United States Pharmacopoeia monograph, which allows for production of WFI by distillation or a purification process proven to be equal to or superior to distillation, and in the Japanese Pharmacopoeia, which allows for distillation or reverse osmosis (RO) followed by ultrafiltration (UF).

In the pharmaceutical industry, distillation has been the dominant method for producing WFI due to its ability to meet the required specifications and in part due to the regulatory environment. However, other industries with a requirement for high quality water, rather than distillation, employ RO and UF to produce water that is equivalent to or of a better quality than WFI described in the Ph. Eur.

✓ summarises current status of alternative methods for producing water of WFI quality, based on scientific data received from the enquiry on non-distillation technologies
✓ reviews all evidence to support a revision of the WFI monograph to allow non-distillation technologies for producing WFI to be included in addition to distillation

Reflection Paper on WFI (2/2)

➢ recognises concerns about microbiological safety
→ not necessarily an issue, provided that microorganisms are suitably controlled and final quality of water is appropriate:
  • Properly operated membrane systems
  • Initial water pre-treatment
  • Additional purification modules
  • System designs to minimise biofilm formation
  • Regular maintenance/sanitisation
  • Continuous in-process control, fixed interval sampling, in-line monitoring of specifications parameters
  • Continuous measurement of physico-chemical parameters (TOC, conductivity, temperature, pressure) → risk mitigation
  • Increased use of rapid microbial enumeration and identification techniques
    (based on general statements from companies)
WFI monograph (0169): Request for Revision

146th Session of the European Pharmacopoeia Commission, June 2013

- Endorsement of Reflection Paper on WFI

- Agreement to work on the revision of the monograph on Water for injections (0169) (WFI) to allow non-distillation technologies for the production of WFI to be included in addition to distillation

- Acknowledgement that design, failure mode and maintenance of water production systems play an important role in ensuring that appropriate water quality is established and maintained → necessity to discuss roles and responsibilities with GMP/GDP Inspectors Working Group and Joint CHMP/CVMP Quality Working Party

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**WFI monograph (0169)**

- **Quality standard**
- Defines quality of WFI in terms of **microbiological** and **physico-chemical** requirements

**PRODUCTION section revision:**

Consequence: **Highly Purified Water (1927)** → to be deleted from the Ph. Eur.

System design, operation, maintenance (validation and monitoring) → **GMP requirements**

**Revision WFI monograph**

**Liaison** with work undertaken by the GMP/GDP Inspectors Working Group with a view to updating the GMP guidance

**Work plan for GMP/GDP Inspectors Working Group for 2014**

**GMP guide : annex 1**

To agree, in consultation with PIC/S, on the best approach to dealing with recurring issues on the interpretation of this annex and whether guidance is needed on biofilms.

7. **Liaison with other groups**
   - European directorate for the quality of medicines and healthcare
     - Reverse Osmosis for production of water for injections
   - Joint CHMP/CVMP Quality Working Party
     - Reverse Osmosis for production of water for injections
Concept paper on the revision of annex 1 of the guidelines on good manufacturing practice – manufacture of sterile medicinal products (EMA/INS/GMP/735037/2014)

...changes that may require new GMP guidance include those for the revision to the Ph. Eur. monograph on methods other than distillation for the production of water for injection.

Revision WFI monograph: current status

- Publication of revised draft monograph Water for Injections (0169) in Pharmeuropa 27.2 (April 2015)
- Publication of background document Reverse osmosis in Ph. Eur. monograph Water for Injections (0169) in Pharmeuropa (Useful information)

Background document for revision of monograph Water for Injections (WFI), based on the Reflection Paper analysed by the European Pharmacopoeia Commission at its HMP Session, June 2013.

1. Introduction – overview of water for injections (WFI)

The production of WFI is described in the European Pharmacopoeia (Ph. Eur.) monograph Water for injections (0168). In this monograph the method of production of WFI is limited to distillation only. This is currently depicted in the production methods described in the USP/NCCLS Water for injections monograph, which allows for production of WFI by distillation or a purification process proven to be equal to or superior to distillation, and in the Japanese Pharmacopoeia, which allows for production of reverse osmosis (RO) followed by ultrafiltration (UF).

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Public enquiry in Pharmeuropa

• We want to hear from you: pharmeuropa.edqm.eu

• Free access (after registration)

According to the Guide for the work of the European Pharmacopoeia:

• comments should be submitted either via the National Pharmacopoeia Authority or via the Ph. Eur. Secretariat (via the EDQM Helpdesk if outside Europe).

• The addresses of the national pharmacopoeia authorities and of the EDQM are published on the Pharmeuropa website under the tab Useful information.

• Comments are to be submitted before the specified deadline (Pharmeuropa 27.2 / 30th June 2015).

• Please refer to the “How to comment” notice available at the top of each published text.

• Further details: http://pharmeuropa.edqm.eu/home/menupage/English/Useful%20Information/ImportantNotice_E.pdf
What’s next?

- Outcome of Pharmeuropa public enquiry: review of comments, discussion in the Ph. Eur. WAT WP
- Discussions with other Groups and Working Parties (alignment of timelines of monograph revision with timelines for the revision of Annex 1 outlined in EMA/INS/GMP/735037/2014)

- Ph. Eur. Commission: adoption (implementation 1 year after)

Acknowledgements

Dr Ged Lee, Chair of the
Ph. Eur. WAT Working Party
All specialists of the
Ph. Eur. WAT Working Party

***

EDQM colleagues:
Emmanuelle Charton
Thomas Hecker
Stephen Wicks
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