PRODUCTION OF WATER FOR INJECTION

BY MEANS OTHER THAN DISTILLATION

(February 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) by 15 April 2019.

Medicines Quality Assurance working documents will be sent out electronically only. They will also be placed on the Medicines website for comment under “Current projects”. If you have not already received our draft working documents, please send your email address (to jonessi@who.int) and we will add you to our electronic mailing list.

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Please send any request for permission to:

Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland, fax: (41 22) 791 4856, email: kopps@who.int.

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**BY MEANS OTHER THAN DISTILLATION**

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<thead>
<tr>
<th>Description of activity</th>
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<tr>
<td>Preparation of the document by Dr A. Van Zyl, following the recommendation of the 53rd WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).</td>
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1. INTRODUCTION

1.1. Water is widely used in the pharmaceutical industry. It is often used as a raw material, an ingredient in formulations, to prepare reagents, in cleaning and in the manufacture of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP).

1.2. Water for pharmaceutical use must meet quality requirements and specifications as published in standards and Pharmacopoeia. Water of required quality for its intended use should be produced by appropriate methods.

2. SCOPE

2.1. This document provides guidance for the production of Water for Injection (WFI) by means other than distillation. The principles may be applied to other qualities of water produced, meeting other specifications.

2.2. The document is not exhaustive, but aims to provide guidance on the main principles to be considered. Other guidelines and literature should also be consulted.

3. MONOGRAPHS

3.1. Manufacturers should have a specification for WFI.

3.2. Monographs for WFI are published in various national Pharmacopoeia, as well as in The International Pharmacopoeia, and provide for the minimum requirements for the quality of WFI.
3.3. WFI should meet the specification as published in current monographs of the Pharmacopoeia, recognized by the Medicines Regulatory Authority.

4. **LIFE CYCLE APPROACH**

4.1. Good practices during each stage of the life cycle in the production and control of WFI should be considered.

4.2. Stages in the life cycle in production include, but are not limited to, the collection and treatment of source water, treatment of potable water used in production of WFI, production of WFI, storage, distribution and use of WFI.

4.3. Principles of risk management and data governance should be implemented in each relevant stage of the life cycle.

5. **RISK ASSESSMENT**

5.1. An appropriate method for the production of WFI should be used.

5.2. Risks and controls should be identified for each stage of the life cycle of the production, storage, distribution, use and control of WFI.

5.3. Risks should be identified and assessed to determination of the scope and extent of validation and qualification of the system, including the computerized system used for the control of production and monitoring of WFI.

5.4. Where production methods other than distillation are used, specific attention should be taken to ensure:

- that there is no risk of contamination of water;
- the appropriateness of user requirement specifications (URS);
- feed-water quality;
- sequence of purification stages required;
- the extent of pre-treatment required;
- appropriately designed and located sampling points;
- controls are in place to prevent dead legs and contamination; and
- in-line monitoring.

6. **CONTROL STRATEGY**

6.1. There should be no risk of contamination of WFI produced, stored or circulated.

6.2. An appropriate control strategy should be defined to ensure that all risks identified are eliminated, or reduced to an acceptable level.

6.3. Special attention should be given to, for example, the selection of components, their material of construction, preventive maintenance, life cycle and sanitization.

6.4. Water-treatment components, storage and distribution systems should be sanitized by appropriate, effective and validated means - at specified intervals.

6.5. The materials of construction for components selected for the production, storage and distribution of WFI systems must not be reactive, additive or absorptive or adversely affect the quality of water produced. Examples of suitable materials include SS 316L, Polyvinylidene Fluoride (PVDF) and Polypropylene (PP).

6.6. The storage and distribution systems should further be designed to permit a validated, routine sanitisation process.

6.7. Treatment (also referred to as pre-treatment) of water entering the system should ensure adequate removal of organic particles, matter and microbiological impurities. The treatment should not have a detrimental effect on materials of construction of the water system.
6.8. Techniques such as deionisation, raw water ultrafiltration, electrolytical scale reduction, water softening, descaling, pre filtration and degasification (can be located between the stages of a double pass reverse osmosis (RO) system) should be considered.

6.9. All parts of the system, including, for example, RO membranes, storage and distribution systems, should be appropriately designed and constructed to allow for routine sanitisation (thermal or chemical, or a combination thereof).

6.10. Special attention should be given to the qualification and validation of the WFI system.

6.11. Appropriate sampling techniques should be used to sample water at defined sampling locations in accordance with a sampling schedule.

7. GOOD PRACTICES IN THE PRODUCTION OF WFI

7.1 WFI should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feedwater.

7.2 An appropriate method should be used to produce WFI. The preferred method is distillation. Alternative methods, such as RO, may be considered.

7.3 Where RO is used, double-pass RO coupled with other appropriate techniques such as electro-deionisation (EDI), ultrafiltration (UF) or nanofiltration, should be considered. The purification process employed should be proven to be equivalent or better than distillation.

7.4 WFI should meet the relevant pharmacopoeia specifications for chemical and microbiological purity (including endotoxin).

7.5 Water testing results should be trended. Trend data should be reviewed routinely in order to determine the potential for deterioration in the system.
7.6 Appropriate action and alert limits should be specified. Alerts should be reassessed routinely to enable, where possible, a re-evaluation of those control limits.

7.7 There should be no risk of recontamination of WFI during production, storage and distribution.

7.8 The system should remain in a validated state throughout its life cycle.

7.9 The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, pH, total organic carbon (TOC) and microbial contamination.

7.10 In-line sampling and testing should be supported by off-line testing.

7.11 RO membranes should be monitored for any potential integrity breaches.

Further reading


International Pharmacopoeia

United States Pharmacopeia

European Pharmacopoeia

ISPE Baseline. Water and Steam systems. Volume 4