World Health Organization

PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION

(July 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by **20 September 2019**.

Working documents are sent out electronically and they will also be placed on the WHO Medicines website (http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/) for comments under the "Current projects" link. If you wish to receive our draft guidelines, please send your email address to jonessi@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/19.786:

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Description of activity	Date
Preparation of the document following recommendation of the Fifty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	December 2018 to January 2019
Mailing of working document inviting comments, including to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP), and posting of the working document on the WHO website for public consultation.	February - March 2019
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	April 2019
Discussion of working document and feedback received during the informal Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	2-3 May 2019
Discussion of working document and feedback received during the informal Consultation on Regulatory Guidance For Multisource Products.	17-18 May 2019
Consolidation of comments received and review of feedback.	June 2019
Discussion of working document and feedback received during the public consultation and the above meetings in the informal	2-5 July 2019

Consultation on Good Practices for Health Products Manufacture and Inspection.	
Mailing of the revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for the second round of public consultation.	July – 20 September 2019
Consolidation of comments received and review of feedbacks. Preparation of working document for discussion.	End of September 2019
Presentation to the Fifty-fourth ECSPP meeting.	14-18 October 2019
Any other follow-up action as required.	

PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION

BACKGROUND

In recent years, several pharmacopoeias adopted revised monographs on water for injection (WFI) allowing production by non-distillation technologies. Until now, the production of WFI in many countries was limited to distillation only. The monograph revisions in a number of pharmacopoeias were the result of extensive consultations with stakeholders and now allow production of WFI by a purification process equivalent to distillation – such as reverse osmosis – coupled with appropriate techniques. During the Fifty-second meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in October 2017, members of the Expert Committee recommended that the WHO Secretariat should collect feedback on whether or not to revise the WHO specifications and good manufacturing practices (GMP) in relation to the production of WFI. In light of this, feedback was sought on whether or not the WHO specifications and GMP text(s) should be revised in relation to the production of WFI, allowing other purification processes and, if yes, whether details on additional requirements should be added and, if so, which requirements these should be. A working document for public inquiry was circulated in March 2018 and comments received were consolidated in April 2018. The issue was discussed at an informal Consultation on Screening Technologies, Sampling and Specifications for Medicines held in May 2018 and then again during an informal Consultation on Good Practices for Health Products Manufacture and Inspection held in July 2018. Comments and feedback were then consolidated before presentation of the document and all comments to the Expert Committee in October 2018.

During the Fifty-third ECSPP meeting, the Expert Committee members discussed and agreed that the monograph in *The International Pharmacopoeia*, Water for Injections (*1*) and WHO Good Manufacturing Practices: Water for Pharmaceutical Use (*2*) be revised to allow different technologies for production of WFI other than distillation.

This specific text was drafted to clarify the use of alternative production of WFI.

PRODUCTION OF WATER FOR INJECTION BY MEANS OTHER THAN DISTILLATION

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 WFI by means other than distillation. The principles described in this guideline may be applied to other grades 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 (*1*,*2*).

3. MONOGRAPHS

3.1. Manufacturers should have appropriate specifications for WFI.

3.2. Monographs for WFI are published in *The International Pharmacopoeia*, as well as various national 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 and purified water used in production of WFI, production of WFI, storage, distribution, control and use of WFI.

4.3. Principles of risk management and data governance should be applied 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 identified should be assessed to determine the scope and extent of validation and qualification of the system, including the computerized system, used for the production, control and monitoring of WFI.

5.4. Where production methods other than distillation are used, specific controls 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. The WFI system should be appropriately qualified and validated.

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

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

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

6.5. Treatment (also referred to as pre-treatment) of water entering the system should ensure adequate removal of chemicals (organic and inorganic), particles, matter and microbiological impurities. The treatment should not have a detrimental effect on materials of construction or downstream components of the water system.

6.6. Techniques such as deionisation, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a double pass reverse osmosis (RO) system).

6.7. The materials of construction of all parts of the system, including components selected for the production, storage and distribution of WFI systems, should be appropriately designed and constructed, should not be reactive, additive, absorptive or adversely affect the quality of water. Examples of suitable materials include SS 316L and a variety of polymers (e.g. Polyvinylidene Fluoride (PVDF) and Polypropylene (PP)).

6.8. These should allow for routine sanitisation (thermal or chemical, or a combination thereof). The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals in accordance with a documented procedure.

6.9. Appropriate sampling techniques should be used to sample water for analysis, at defined sampling locations, in accordance with a documented sampling procedure and a schedule.

7. GOOD PRACTICES IN THE PRODUCTION OF WFI

7.1 WFI should be prepared either from water that complies with WHO guidelines for drinking-water, national standards for drinking water or purified water as a minimum quality feedwater.

7.2. An appropriate method should be used to produce WFI.

7.3 Where RO is used, single or 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 at least equivalent to 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 in addition to specification limits should be specified. Alert and action limits should be reassessed routinely to enable, where possible, a re-evaluation of those control limits.

7.8 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.

7.9 A combination of online and offline monitoring of WFI should be done to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with on-line instruments.

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

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

References

1. *The International Pharmacopoeia*, 8th edition, 2018 (update in progress).

2. WHO Good Manufacturing Practices: Water for Pharmaceutical Use, WHO Technical Report Series, No. 970, Annex 2. 2011 (update in progress).

Further reading

ISPE Baseline. Water and Steam Systems. Volume 4

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