Annex 3

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), intermediates and finished pharmaceutical products.

1.2 Water for pharmaceutical use must meet quality requirements and specifications, as published in relevant standards and pharmacopoeias. Water of the 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 described in this guideline may be applied to other grades of water, 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* (*1*), as well as various national pharmacopoeias, 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 relevant pharmacopoeia recognized by the national medicines regulatory authority.

4. Life-cycle approach

4.1 Good practices during each stage of the life-cycle of WFI should be considered.

4.2 Stages include, but are not limited to, the collection and treatment of source water; treatment of drinking water; treatment of purified water; and the production, storage, distribution, use and control of WFI.

4.3 Principles of risk management (*3*) 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 analysed and evaluated to determine the scope and extent of validation and qualification of the system, including the computerized controls used for the production, control and monitoring of WFI. Risk management should be an ongoing part of the quality management process for WFI. A mechanism to review or monitor events associated with production, storage, distribution and use of WFI should be implemented.

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

- the appropriateness of user requirement specifications;
- feed-water quality;
- the sequence of purification stages required;
- the extent of pretreatment required;
- appropriately designed and located sampling points;
- controls are in place to prevent "dead legs"; and
- in-line monitoring.

6. Control strategy

6.1 The WFI system should be appropriately qualified and validated.

6.2 There should be controls to minimize the 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 All parts of the system (pretreatment, treatment, storage and distribution) should be appropriately designed and constructed. Materials for construction should not be reactive, additive, absorptive or adversely affect the quality of water and should be suitable for the sanitizing method used.

6.5 Treatment (also referred to as pretreatment) 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 the materials of construction or downstream components of the water system.

6.6 Techniques such as deionization, electro-deionization, nanofiltration, ultrafiltration, water softening, descaling, prefiltration, degasification, and ultraviolet treatment, along with other techniques, may be considered in conjunction with a single- or double-pass reverse osmosis system.

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

6.8 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 water for injection

7.1 WFI should be prepared either from water that complies with World Health Organization guidelines for drinking water (*4*), national standards for drinking water as a minimum quality feedwater, or purified water.

7.2 The results of water testing should be trended. Trend data should be reviewed routinely, in order to determine the potential for deterioration in the system.

7.3 Appropriate alert and action limits, in addition to specification limits, should be specified. Trend data should be assessed routinely and used to revise limits where appropriate.

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

7.5 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 online instruments. Use of rapid microbiological methods is encouraged for timely monitoring, and aids with rapid responses to prevent deterioration of the system.

7.6 The outlet of reverse osmosis systems should be monitored, to ensure that potential breaches are identified. This may include monitoring the conductivity of the water, and pressure.

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

References

1. The International Pharmacopoeia, 9th ed. Geneva: World Health Organization; 2019 (https://apps.who.int/phint/en/p/docf/, accessed 4 December 2019).
2. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; http://apps.who.int/medicinedocs/documents/s19832en/s19832en.pdf, accessed 4 November 2019).
3. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 4 December 2019).
4. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=60F04022DD9AD3A4C214F236B00A5F52?sequence=1, accessed 4 December 2019).

Further reading

- Augustine R, Baird A, Bevilacqua A, Cohen N, Coleman RC Evans J et al. ISPE baseline guide volume 4. Water and steam systems, 3rd ed. North Bethesda (MD): International Society for Pharmaceutical Engineering; 2019.