DRAFT WORKING DOCUMENT FOR COMMENTS:

Good manufacturing practices: water for pharmaceutical use

Please send your comments to Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (kopps@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) before 30 June 2020. Please use our attached Comments Table for this purpose.

Our 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 all 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/20.842:

**Good manufacturing practices:**
**water for pharmaceutical use**

<table>
<thead>
<tr>
<th>Description of activity</th>
<th>Date</th>
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<tbody>
<tr>
<td>Preparation of the document following recommendation of the Fifty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).</td>
<td>February- April 2020</td>
</tr>
<tr>
<td>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.</td>
<td>May 2020</td>
</tr>
<tr>
<td>Consolidation of comments received and review of feedback. Preparation of working document for discussion.</td>
<td>June 2020</td>
</tr>
<tr>
<td>Discussion of working document and feedback received during the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines, replaced by virtual meetings.</td>
<td>June 2020</td>
</tr>
<tr>
<td>Preparation of working document for next round of public consultation.</td>
<td>July 2020</td>
</tr>
<tr>
<td>Mailing of the revised working document inviting comments, including to the EAP, and posting the working document on the WHO website for a second round of public consultation.</td>
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</tr>
<tr>
<td>Consolidation of comments received and review of feedback by a sub-team composed of the participants of the virtual meetings. Preparation of working document for discussion.</td>
<td>September 2020</td>
</tr>
<tr>
<td>Presentation to the Fifty-fifth ECSPP meeting.</td>
<td>12-16 October 2020</td>
</tr>
<tr>
<td>Any other follow-up action as required.</td>
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</tbody>
</table>
Good manufacturing practices: water for pharmaceutical use

Background

The control of water quality, including microbiological and chemical quality, throughout production, storage and distribution processes is a major concern. Unlike other product and process ingredients, water is usually drawn from an on-demand system and is not subject to testing and batch or lot release prior to use. The assurance of water quality to meet the on-demand expectation is, therefore, essential.

In recent years, following extensive consultation with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies, such as reverse osmosis (RO). In 2017, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat collect feedback on whether or not they should revise the WHO specifications and good manufacturing practices (GMP) on WFI, and how to do so. Following discussions during several consultations, the ECSPP agreed that the monograph in *The International Pharmacopoeia (Water for injections)* and the guideline *WHO Good manufacturing practices: water for pharmaceutical use (1)* should both be revised to allow for technologies other than distillation for the production of WFI. In early 2019, the WHO Secretariat commissioned the preparation of a draft guidance text for the production of WFI by means other than distillation. Following several public consultations, the text was presented to the Fifty-fourth ECSPP. The Expert Committee adopted the *Production of water for injection by means other than distillation* guideline and recommended that it should also be integrated into WHO’s existing guideline on *Good manufacturing practices: water for pharmaceutical use*.


1. Introduction
2. Background to water requirements and uses
3. General principles for pharmaceutical water systems
4. Water quality specifications
   4.1. Pharmacopoeial specifications
   4.2. Drinking-water
   4.3. Bulk purified water
   4.4. Bulk highly purified water
   4.5. Bulk water for injections
   4.6. Other grades of water
5. General considerations for water purification systems
6. Water storage and distribution systems
7. Good practices for water systems
8. System sanitization and bioburden control
9. Storage vessels
10. Water distribution
11. Biocontamination control techniques
12. Operational considerations
   12.5 Phase 1
   12.6 Phase 2
   12.7 Phase 3
13. Continuous system monitoring
14. Maintenance of water systems
15. System reviews
16. Inspection of water systems
References
Further reading
1. Introduction and scope

1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It intends to provide information about different specifications for WPU; guidance on GMP regarding the quality management of water systems; water treatment (production) systems; water storage and distribution systems; qualification and validation; and sampling, testing and the routine monitoring of water.

1.2 Although drinking-water is addressed, the focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications.

1.3 This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

1.4 The document can be used in whole or in part, as appropriate, to the section and application under consideration.

1.5 In addition to this document, the “Further reading” section at the end of this document includes some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

1.6 This document is supplementary to the World Health Organization (WHO) Good manufacturing practices for active pharmaceutical ingredients (2), and WHO Good manufacturing practices for pharmaceutical products: main principles (3).

2. Background to water requirements and uses

2.1 Water is a widely used substance in the pharmaceutical industry. It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing). Water
has unique chemical properties due to its polarity and hydrogen bonds. It is able to dissolve, absorb, adsorb or suspend different compounds. These would include contaminants that may represent hazards in themselves or that may be able to react with intended product substances, resulting in hazards to health. Water should therefore meet the required quality standards to mitigate these risks.

2.2 The microbiological and chemical quality of water should be controlled throughout the production, storage and distribution of water. Water is not usually subjected to testing and batch or lot release before use. It is usually drawn from a system on-demand for use. Results from testing are normally available only after water has already been used as microbiological tests may require periods of incubation. The assurance of quality to meet the on-demand expectation of water is therefore essential.

2.3 To reduce the risks associated with the production, storage and distribution of water and, considering the properties and use of water, it is essential:

- to ensure the appropriate design, installation, operation and maintenance of the pre-treatment (production of drinking-water), treatment (production of WPU such as purified water (PW) and WFI), and storage and distribution systems;
- to perform periodic sanitization;
- to take the appropriate measures in order to prevent chemical and microbial contamination; and
- to prevent microbial proliferation.

2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification, should be used for the intended application.

3. General principles for pharmaceutical water systems

3.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of intended quality.
3.2 The capacity of these systems should be appropriate to meet the average and peak flow demand. The systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.

3.3 The use of the systems following an initial qualification such as installation qualification (IQ), operational qualification (OQ), performance qualification (PQ) and validation should be approved by the quality unit, e.g. quality assurance (QA).

3.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, as appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.

4. Water quality specifications

4.1 Pharmacopoeial specifications

4.1.1 Pharmacopoeias include specifications for both bulk and dosage form types of water. Where this document refers to specifications, such as the pharmacopoeias, the relevant, current publications should be used. This document does not attempt to duplicate such material. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer should choose the appropriate specification in accordance with the related marketing authorization submitted to the relevant medicine’s regulatory authority. Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias (4) and limits for various impurities or classes of impurities are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological quality of water.
4.2 Drinking-water

4.2.1 The quality of drinking-water is covered by the WHO drinking-water quality guidelines (5) and standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the competent authority.

4.2.2 Drinking-water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and the sea. The condition of the source water should be considered when choosing a treatment to produce drinking-water. A typical treatment would include desalinization, softening, removal of specific ions, particle reduction and antimicrobial treatment.

4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free of any defects that could lead to contamination of any product.

4.2.4 Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. The appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water from the water source. Where required, the quality may be achieved through appropriate processing on-site.

4.2.5 Where drinking-water is purchased in bulk and transported to the user by water tanker, controls should be put in place to mitigate any risks associated therewith. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a way similar to that used for any other starting material.

4.2.6 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the PW treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is
achieved should be identified and a water sample taken and tested at defined intervals thereafter.

4.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feedwater for the production of higher qualities of WPU, then testing should be carried out periodically by the water user’s site to confirm that the quality meets the standards required for drinking-water.

4.2.8 Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.

4.2.9 Examples of typical processes employed to produce drinking-water may include:
- desalination;
- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite {chlorine} injection);
- iron (ferrous) removal;
- precipitation; and
- the reduction of concentration of specific inorganic and/or organic materials.

4.2.10 Controls should be implemented to prevent the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include backflushing, chemical and/or thermal sanitization and frequent regeneration.

4.2.11 The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.

4.2.12 Where drinking-water is stored and distributed by the user, the storage and distribution systems should not allow the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance
with a defined procedure. The storage and distribution of drinking-water should be
done in a manner to ensure a turnover or recirculation of the stored water sufficient
enough to prevent stagnation.

4.2.13 The equipment and systems used to produce and store drinking-water should be able
to be drained and sanitized.

4.2.14 Storage tanks should be closed with appropriately protected vents and should allow
for visual inspection.

4.2.15 Distribution pipework should be able to be drained or flushed and sanitized.

4.2.16 The scope and extent of qualification for the system should be identified and justified.

4.2.17 The results from testing drinking-water should be subjected to statistical analysis in
order to identify trends and changes. If the drinking-water quality changes
significantly, but is still within specification, the direct use of this water as a WPU, or
as the feedwater to downstream treatment stages, should be reviewed for any risks
and the results of the review and action to be taken and documented.

4.2.18 Changes to a system or to its operation should be made in accordance with change
control procedures.

4.2.19 Additional testing should be considered if there is any change in the raw water source,
treatment techniques or system configuration.

4.3 Bulk purified water

4.3.1 Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications
for chemical and microbiological purity.

4.3.2 BPW should be prepared from drinking-water as a minimum-quality feedwater.
4.3.3 Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW may be prepared by, for example, a combination of ion exchange, RO, RO/electro-deionization (EDI), ultrafiltration and vapour compression.

4.3.4 The following should be considered when configuring a water purification system or defining user requirement specifications (URS):

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- energy consumption;
- appropriately located sampling points designed in such a way so as to avoid potential contamination; and
- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

4.3.5 Ambient-temperature systems such as ion exchange, RO and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization, at defined intervals, as well as other controls, should be defined to prevent and minimize microbiological contamination.

4.3.6 Appropriate, validated methods for sanitizing each stage of purification needs to be in place. Where agents are used for sanitization, their removal must be proven.

4.3.7 The following controls should be considered:

- the maintenance of water flow at all times, in order to prevent water from stagnating;
- control of temperature in the system by heat exchangers or plant room cooling in order to reduce the risk of microbial growth (guidance value < 25 °C);
- the provision of ultraviolet disinfection at appropriate locations in the system;
• the use of water-treatment system components that can periodically be thermally sanitized;
• in addition to thermal sanitization, the application of chemical sanitization such as ozone, hydrogen peroxide and/or peracetic acid; and
• thermal sanitization at > 70 °C.

4.3.8 BPW should have the appropriate action and alert limits for microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

4.4 Bulk highly purified water

4.4.1 Bulk highly purified water (BHPW) must meet the same quality standards as WFI, including the limit for endotoxins.

4.4.2 BHPW should be prepared from drinking water as a minimum-quality feedwater.

4.4.3 Any appropriate and qualified purification technique, or sequence of techniques, may be used to prepare BHPW. BHPW is often produced by double pass RO coupled with other suitable techniques such as ultrafiltration and deionization.

4.4.4 BHPW should also be protected from recontamination and microbial proliferation.

4.4.5 BHPW and WFI have identical microbiological requirements.

Note: The guidance provided in section 4.3 for BPW is equally applicable to BHPW.

4.5 Bulk water for injections

4.5.1 Bulk water for injections (BWFI) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.
4.5.2 BWFI is not sterile water and is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

4.5.3 As a robust technique should be used for the production of BWFI, the following should be considered when designing a water purification system:

- the quality of feedwater (e.g. drinking-water, usually with further treatment, or PW);
- the required water quality specification;
- the quantity of water;
- based on the selection of components and type of system, the appropriate URS, qualification and validation;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions; and
- cool-down venting to avoid contamination ingress.

4.5.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, techniques such as deionisation, electro deionization, nano filtration, ultrafiltration, water softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system.

4.5.5 BWFI should have the appropriate action and alert limits and should also be protected from recontamination and microbial proliferation.

Note: For a full description, see *Production of water for injection by means other than distillation.*

[Note from Secretariat: the text published in the WHO Technical Report Series, No. 1025, 2020, Annex 3 will be attached as Annex 1 to this text.]

4.6 Other grades of water

When a specific process requires a special non-pharmacopoeial grade of water, its specification must be documented within a company’s quality system. As a minimum, it must
meet the pharmacopoeial requirements relating to the grade of WPU required for the type of dosage form or process step.

5. **General considerations for water purification systems**

5.1 Pharmaceutical manufacturers should apply the current principles of quality risk management (6) in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used.

5.2 Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.

5.3 Risks identified should be analyzed and evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.

5.4 Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.

5.5 Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be done where changes and deviations are managed.

5.6 The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of an intended grade. Based on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:

- the quality of the available feedwater and the variation over time (seasonal changes);
- the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
427  • the extent of pre-treatment required;
428  • the sequence of purification steps required;
429  • the design and location of sampling points;
430  • the sanitization strategy;
431  • the availability of water-treatment equipment on the market;
432  • the reliability and robustness of the water-treatment equipment in operation;
433  • the yield or efficiency of the purification system;
434  • the ability to adequately support and maintain the water purification equipment;
435  • the continuity of operational usage considering hours/days/years and planned downtime;
436  • the total life-cycle of the system (including capital, operation and maintenance);
437  • the final water quality specification; and
438  • the quantity of water required by the user.
439
440  5.7 The specifications for water purification equipment, storage and distribution systems should take into account the following:
441  • the location of the plant room;
442  • the extremes in temperature that the system will encounter;
443  • the risk of contamination, for example, from materials of construction (contact materials) and the environment;
444  • the adverse impact of adsorptive contact materials;
445  • hygienic or sanitary design, where required;
446  • corrosion resistance;
447  • freedom from leakage;
448  • system configuration to avoid proliferation of microbiological organisms;
449  • tolerance to cleaning and sanitizing agents (thermal and/or chemical);
450  • the sanitization strategy;
451  • system capacity and output requirements; and
452  • the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.
The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the ability to collect samples;
- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

6. Water storage and distribution systems

Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking-water.

The water storage and distribution systems for PW, BHPW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

7. Good practices for water systems

The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and should satisfy the following objectives for the full range of the working temperature and potential chemicals that will come into contact with the system at rest, in operation and during sanitization. The construction materials should be of an appropriate quality.

As a minimum, the following should be considered:

- Compatibility and suitability.
- No leaching, adsorbing and absorbing.
- Corrosion resistance.
- Materials of construction: the materials used should be appropriate, for example, sanitary specification plastics such as polypropylene, polyvinylidene-difluoride and
perfluoro alkoxy. Other materials, such as unplasticized polyvinyl-chloride (uPVC), may be used for treatment equipment designed for less pure water such as ion exchangers and softeners. Plastics used should be manufactured from materials that should at least meet the minimum food grade standards, be non-toxic and be compatible with all chemicals used. Their chemical and biological characteristics should meet any relevant pharmacopoeial specifications or recommendations. Stainless-steel grade 316L or higher is generally recommended. The choice of material should take into account the intended sanitization method.

- Passivation: passivation should be considered after initial installation and after significant modification in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.

- Smooth internal finish: internal finish should be smooth in order to prevent the formation of biofilms and corrosion (e.g. an arithmetical average surface roughness of not greater than 0.8 micrometre (Ra); mechanical and electro-polishing of stainless steel).

- Jointing: the manner in which pieces are jointed should be appropriate and controlled. Where welding is used, the process should include, as a minimum, the qualification of the operator, documentation of the welder set-up, work session test pieces (coupons or weld samples), logs of all welds and records (e.g. photographs or videos) of visual inspection of a defined proportion of welds (e.g. 100% hand welds or 10% automatic welds). Threaded connections should be avoided.

- Flanges, unions and valves: where flanges, unions or valves are used, they should be of a hygienic or sanitary design. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.

- Documentation: all system components should be fully documented and be supported by original or certified copies of material quality certificates. Where these are not available or traceable, on-site tests should be performed and test reports should be available. All documentation related to the qualification and validation of the system should be available. Documents should include, as a minimum, system drawing, isometric drawings, specifications for components, qualification and validation protocols and reports, calibration certificates.
8. **System sanitization and bioburden control**

8.1 Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.

8.2 Validated, detailed procedures for sanitizing all relevant parts of the system should be followed. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.

8.3 Systems that operate and are maintained at elevated temperatures (e.g. > 65) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms (see section 9.2 for guidance).

8.4 Where the chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.

8.5 Records of sanitization should be maintained.

9. **Storage vessels**

9.1 Storage vessels installed and used later should be appropriate for their intended use.

9.2 As a minimum, the following should be considered:

- the design and shape;
- the provision for drainage of water from the vessel, when required;
- construction materials;
• capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
• prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate);
• the need for the use of a spray-ball or distributor devices to wet the inner surfaces of the vessel;
• limitation and design of nozzles within the storage vessels;
• the fitting of heated, bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
• the fitting of pressure-relief valves and bursting discs which are of a sanitary design (bursting discs should be provided with external rupture indicators to ensure that loss of system integrity is detected);
• the design and sanitation, as required, of level indicators;
• the design and location of valves, sampling points and monitoring devices and sensors; and
• the need for heat exchangers or jacketed vessels. Where these are used, controls should be put in place in order to ensure that there is no risk of contamination of water.

10. Water distribution

10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW, BHPW and BWFI. Where this is not the case, a good justification for using a non-recirculating one-way system should be provided.

10.2 As a minimum, the following should be considered:
• controls to prevent proliferation of contaminants;
• the length of the distribution system;
• material of construction, joints and impact as a result of sanitization; and
• design and location of devices, sensors and instruments such as flow meters, total organic carbon (TOC) analysers and temperature sensors;

10.3 Filtration should not usually be used in distribution loops or at take-off user points as these are likely to conceal system contamination.

10.4 Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken in order to prevent the heating or cooling utility from contaminating the water.

10.5 Secure types of heat exchangers, such as double tube plate, double plate and frame, or tube and shell configuration, should be considered. Where these types are not used, an alternative approach whereby the utility is maintained and monitored at a lower pressure than the WPU may be considered. The latter approach is not usually appropriate in BWFI systems.

10.6 Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.

10.7 When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

10.8 Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.

10.9 Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

10.10 Consideration should be given to preventing contamination in systems where parallel pumps are used, especially if there is stagnant water when one of the pumps is not being used.
11. Biocontamination control techniques

11.1 Water purification systems should be sanitized using chemical and or thermal sanitization procedures as appropriate (e.g. production, storage and distribution). The procedure and conditions used, such as times and temperatures, should be suitable.

11.2 Other control techniques to be considered include:

- The maintenance of a continuous circulation of water: a turbulent flow of 1.2 m/s, for example.
- Ensuring the shortest possible length of pipework.
- Isolating pipework for ambient temperature systems from adjacent hot pipes.
- Minimizing dead legs, including in the pipework, through the appropriate design. Dead legs are measured and calculated and, as a guide, should not exceed three times the branch diameter (3D).
- Separate pressure gauges from the system by membranes.
- Using hygienic pattern diaphragm valves.
- Installing pipework to allow for full drainage. A guidance figure for the slope is 1:100.
- Considering ultraviolet radiation sources in pipework and maintaining the system at an elevated temperature (e.g. >65 °C).
- Periodic sanitization by suitable means, e.g. hot water (guidance temperature > 70 °C), super-heated hot water or clean steam, and/or routine chemical sanitization using ozone or other suitable chemical agents.

11.3 When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water.

12. Operational considerations

12.1 Water systems should be appropriately qualified and validated (7). The scope and extent of qualification should be determined based upon risk assessment.
12.2 There should be documented evidence of consideration and execution of stages of qualification including, as appropriate, URS, factory acceptance testing (FAT), site acceptance testing (SAT), design qualification (DQ), IQ, OQ and PQ.

12.3 Commissioning work done should be documented. Commissioning is not a replacement for qualification.

12.4 In order to validate the reliability and robustness of a system and its performance, a three-phase approach should be used over an extended period of time. Tests on the source water (drinking-water) should be included within the validation programme and continued as part of the routine monitoring, and these results should meet specifications.

12.5 Phase 1

Phase I should cover a period of at least two weeks. The system should be monitored intensively for its performance. The system should operate continuously without failure or performance deviation. Normally, water should not be used for FPP manufacturing during this phase.

The procedures and protocols for Phase I should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feedwater daily to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points;
- develop the appropriate operating ranges;
- develop and finalize the operating, cleaning, sanitizing and maintenance procedures;
- demonstrate the production and delivery of product water of the required quality and quantity;
- use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting;
- verify provisional alert levels; and
- develop and refine test-failure procedure.
12.6 Phase 2

Phase 2 should cover at least a further test period of two weeks. The system should be monitored while deploying all the refined SOPs after the satisfactory completion of Phase 1. The sampling program should be generally the same as in Phase 1. The use of the water for FPP manufacturing purposes during this phase may be acceptable, provided that both commissioning and Phase 1 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:

- demonstrate consistent operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

12.7 Phase 3

Phase 3 should cover at least a further 12 months after the satisfactory completion of Phase 2. The sample locations, sampling frequencies and tests may be reduced to the normal routine pattern based on the established procedures proven during Phase 1 and Phase 2. After completion of the qualification and validation programme of Phase 3, a system review should be undertaken. This may include the trending of results and the evaluation of system performance capability. The appropriate action should be taken where identified.

Water can be used during this phase (e.g. for manufacturing and cleaning) which has the following objectives:

- to demonstrate a reliable performance over an extended period of time; and
- to ensure that seasonal variations are evaluated.

13. Continuous system monitoring

13.1 The system should be subject to continuous monitoring.
13.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.

13.3 A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, temperature, conductivity and TOC should be monitored with online devices with periodic offline testing to confirm the results. Other parameters may be monitored through offline testing.

13.4 Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined programme.

13.5 Offline samples should be taken from points of use or dedicated sample points where points of use cannot be sampled. All water samples should be taken using the same methodology as detailed in production procedures, e.g. with a suitable flushing and drainage procedure in place.

13.6 Tests should be carried out to ensure that the approved pharmacopoeial specification (and company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.

13.7 Monitoring data should be subjected to trend analysis, e.g. monthly, quarterly and annually. The results should be within defined control limits, such as 2 or 3 sigma.

13.8 Alert and action levels should be established based on historically reported data.

13.9 Trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective actions.

14. Maintenance of water systems

14.1 WPU systems should be maintained and recorded in accordance with an approved and documented maintenance programme.
The programme should take into account at least the following:

- defined frequency for system elements;
- the calibration programme;
- SOPs for specific tasks;
- control of approved spares;
- preventive maintenance and maintenance plan and instructions;
- a review and approval of systems for use upon completion of work; and
- a record and review of problems and faults during maintenance.

## 15. System reviews

### 15.1 WPU systems should be reviewed at described intervals.

### 15.3 The review team should be comprised of representatives from engineering, utilities, validation, QA, quality control, microbiology, production and maintenance, and so on.

### 15.3 The review team should consider matters such as:

- changes made since the last review;
- system performance and capability;
- reliability;
- quality trends;
- failure events and alarms;
- investigations;
- out-of-specification and out-of-limit results;
- compliance with current GMP requirements for WPU systems;
- documentation being a current reflection of the WPU system;
- records including log books and electronic data;
- the current SOPs relating to WPU; and
- the computerized system linked to the water system, e.g. SCADA (Supervisory Control and Data Acquisition).
15.4 The application of specific types of water to processes and dosage forms should be considered.

15.5 Pharmaceutical manufacturers should use the appropriate grade of WPU during, for example, the manufacture of APIs and different dosage forms; for different stages in washing and cleaning; in the preparation of reagents and solutions; and in the synthesis of materials and products.

15.6 The grade of water used should take into account the nature and intended use of the intermediate or finished product and the stage in the manufacturing process at which the water is used.

15.7 BHPW can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeia monographs for BWFI.

15.8 BWFI should be used, for example, in the manufacture of injectable products, such as dissolving or diluting substances or preparations during the manufacturing of parenteral products, and for the manufacture of sterile water for preparation of injections. BWFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

15.9 When steam comes into contact with an injectable product in its final container or with equipment for preparing injectable products, it should conform to the specification for BW when condensed.

16. Inspection of water systems

16.1 WPU (BPW, BHPW and BWFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audits and self-inspection of established water systems.
16.2 This document can be used as the basis of an audit and inspection. A tour of the water system, treatment system, storage and distribution system, as well as visible pipework and user points, should be performed to ensure that the system is appropriately designed, installed, qualified, validated, maintained and monitored.

16.3 The following items could be included in an audit or inspection:

• a review of current drawings of the water system showing all components in the system from the inlet to the points of use, along with sampling points and their designations;

• a physical check to ensure that the system matches the piping and instrumentation diagram or drawing (P&ID);

• approved piping drawings (e.g. orthographic and/or isometric);

• qualification and validation protocols, reports and results;

• a sampling and monitoring plan with a drawing of all sample points with evidence of sample management, sample preparation, testing and results;

• a training programme for sample collection and testing;

• the setting and monitoring of alert and action levels;

• monitoring of results and evaluation of trends;

• absence of leaks;

• a review of any changes made to the system since the last audit or inspection;

• a review of deviations recorded and their investigation;

• a general inspection of the system for status and condition;

• a review of maintenance, failure and repair logs;

• a check of calibration and standardization of critical instruments and devices;

• a review of the performance capability of the system; and

• procedures and records for sanitization.
References


Further reading

Will be updated further


• European Pharmacopoeia: see website for the publishers of the European Pharmacopoeia and supplements (http://www.pheur.org/).


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