World Health Organization

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 **11 September 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/Rev.1:

Good manufacturing practices: water for pharmaceutical use

Description of activity	Date
Preparation of the document following recommendation of the Fifty-fourth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	February- April 2020
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.	May 2020
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	June 2020
Discussion of the feedback received and the working document with a working group of inspectors during virtual meetings in lieu of the planned Consultation on Good Practices For Health Products Manufacture and Inspection.	28 and 29 July 2020
Preparation of working document for next round of public consultation.	July 2020
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.	August 2020
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.	September 2020
Presentation to the Fifty-fifth ECSPP meeting.	12-16 October 2020
Any other follow-up action as required.	

Good manufacturing practices: water for pharmaceutical use

Background

Water quality, including microbiological and chemical quality, throughout production, storage and distribution processes, should be controlled. 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 consultations with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies. 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*.

This current document is a revision of *WHO Good manufacturing practices: water for pharmaceutical use*, previously published in the WHO Technical Report Series, No. 970, Annex 2, 2011.

1. Introduction
2. Background to water requirements and uses
3. General principles for pharmaceutical water systems

1. Introduction and scope

1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for quality management of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.

1.2 The focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications. It excludes the production, storage and usage of water in quality control laboratories.

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 operating 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 the *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 and other establishments involved in manufacturing pharmaceutical products. 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. These include a relatively high boiling point, high specific heat, cohesion, adhesion and density. These 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 production, storage and distribution. 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. While chemical test results can normally be obtained without delay, results from microbiological 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, it is essential:

- to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage and distribution systems;
- to continuously or periodically perform sanitization;
- to take the appropriate measures in order to prevent chemical and microbial contamination; and
- to prevent microbial proliferation and endotoxin formation, where applicable.

2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification (such as described in a pharmacopoeia), should be used for the intended application.

2.5 The application of specific types of water to processes and dosage forms should be considered.

2.6 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, and in the synthesis of materials and products.

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

2.8 Bulk water for injections (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 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.

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. These 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 Following an initial qualification such as installation qualification (IQ), operational qualification (OQ), performance qualification (PQ) and validation, the release and use of the system 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, where 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 water used in bulk and in dosage forms. Where this document refers to specifications, such as those in 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 and chemical quality of water.

4.2 Drinking-water

Note: The requirements for the design, construction and commissioning of drinking water systems are usually controlled through local regulations. Drinking water systems are not usually qualified or validated.[1]

4.2.1 The quality of drinking-water is covered by the *WHO guidelines for drinking-water quality (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.

[1] See documents listed under Further reading

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.

4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free from any defects that could lead to the 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 the 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 into 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 purified water (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; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on risk assessment.

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});
- 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 minimize 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 water, if possible.

4.2.13 The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, 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 commissioning and 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 potential risks. The appropriate action should 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, reverse osmosis (RO), RO/electro-deionization (EDI), and ultrafiltration.

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;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;

- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;
- material of construction;
- sanitization strategy;
- main components;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

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 (e.g. based on the data collected from the system validation and system behaviour), as well as other controls, should be defined to prevent and minimize microbiological contamination.

4.3.6 Methods for sanitizing each stage of purification should be appropriate and validated. Where agents are used for sanitization, their removal should be validated.

4.3.7 The following controls should be considered in order to minimize and prevent microbial contamination:

- the maintenance of water flow at all times in order to prevent water from stagnating;
- control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
- the provision of ultraviolet disinfection at appropriate locations in the system;
- the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or chemically sanitized using, for example, ozone, hydrogen peroxide and/or peracetic acid; and
- a combination of thermal and chemical sanitization, if required.

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

4.4 Bulk water for injections

4.4.1 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

4.4.2 BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

4.4.3 As a robust technique should be used for the production of BWFI, the following should be considered when configuring a water purification system or defining 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, where appropriate;
- based on the selection of components, material of construction 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;
- cool-down venting to avoid contamination ingress;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- appropriate instrumentation to measure parameters as required;
- sanitization strategy;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.4.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. 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. For full details, see *Production of water for injection by means other than distillation* as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 *(6).*

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

4.5 Other grades of water

4.5.1 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 *(7)* 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 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 carried out 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 the 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);
- the extent of pre-treatment required;
- the sequence of purification steps required;
- the design and location of sampling points;
- the sanitization strategy;
- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;
- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

5.7 The specifications for water purification equipment, storage and distribution systems should take into account the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;

- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- 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.

5.8 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

6.1 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.

6.2 The water storage and distribution systems for PW 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

7.1 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.

7.2.1 As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

Materials of construction should be selected based on the following requirements:

- ability to operate at the temperatures/pressures required;
- lack of impact to the final water quality;
- resistant to any sanitizing chemicals that may be used;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced/adequately maintained.

For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage.

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or PVDC is generally recommended. The choice of material should take into account the intended sanitization method.

- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, welder set-up, work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% manual welds, 10% orbital welds).
- Joints should be made using sanitary connections, for example, Tri-clover joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (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.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micron for PW and WFI systems and are typically installed between process stages and on the distribution loop return. 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.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.
- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for on-line measurement for total organic carbon (TOC), conductivity and temperature.
- Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining

records, calibration certificates, system pressure test records and records of passivation.

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 Controls may include 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, as well as the frequency, should be defined and proven to be effective for sanitizing all relevant parts of the system. 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. > 70 °C) 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.

8.6 Other control techniques to be considered may include:

- The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000.

- Ensuring hygienic design, including the use of zero dead leg diaphragm valves and minimizing dead legs. Areas of possible dead legs should be measured and calculated.
- Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1:100.
- Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
- Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

9. Storage vessels

9.1 Storage vessels 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) and 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 bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
- the fitting of sanitary design bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
- the design and sanitization, 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, double tube sheet or double plate heat exchangers should be used, ideally with the utility pressure less than the system pressure to minimise the risk of contamination.

10. Water distribution

10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.

10.2 As a minimum, the following should be considered:

- controls to minimize proliferation of contaminants;
- material of construction, joints and impact as a result of sanitization; and
- the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analysers and temperature sensors.

10.3 Filtration should not be used in distribution loops or at take-off user points.

10.4 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.

10.5 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.

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

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

10.8 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. Operational considerations including some qualification and validation principles

11.1 Water systems should be appropriately qualified and validated *(8)*. The scope and extent of qualification should be determined based on risk assessment.

11.2 When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.

11.3 In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. 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.

Phase 1

Phase I should cover a period of at least two weeks.

Operational procedures and schedules 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 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 including the end of the distribution loop;
- verification of operating ranges;
- demonstrate performance of operating, cleaning, sanitizing and maintenance procedures;

- demonstrate the consistent production and delivery of product water of the required quality and quantity;
- provisional alert and action levels; and
- test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.

Phase 2

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

The approach should also:

- demonstrate consistent system 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.

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 according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified.

Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

12. Continuous system monitoring

12.1 The system should be subject to continuous monitoring.

12.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.

12.3 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.

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

12.5 Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.

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

12.7 The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.

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

12.9 Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions.

13. Maintenance of water systems

13.1 WPU systems should be maintained in accordance with an approved and documented maintenance programme. Records should be kept.

13.2 The programme should take into account at least the following:

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

14. System reviews

14.1 WPU systems should be reviewed at described intervals.

14.2 The review team should be comprised of representatives from, for example, engineering, utilities, validation, QA, quality control, microbiology, production and maintenance.

14.3 Examples of matters to be included in the review are:

- changes made since the last review;
- system performance trends and capability;
- quality trends;

- failure events and alarm history;
- investigations;
- out-of-specification and out-of-limit results;
- alert and action limits;
- assessing compliance with current GMP requirements for WPU systems;
- verification of documentation being current;
- records such as log books and electronic data; and
- the appropriateness of the software and the computerized system linked to the water system, for example, SCADA (Supervisory Control and Data Acquisition), including audit trail, authorized users with access and privileges.

15. Inspection of water systems

15.1 WPU (BPW and BWFI) systems are subjected to regulatory inspections. Users should conduct audits and self-inspection of water systems at regular intervals. Records should be maintained.

15.2 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.

Glossary

Commissioning. The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

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Further reading

[Note from WHO Secretariat: will be updated further]

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