WHO GOOD MANUFACTURING PRACTICES: WATER FOR PHARMACEUTICAL USE

REVISED DRAFT FOR COMMENTS

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We will now send out our working documents electronically and they will also be placed on the Medicines web site for comment. If you do not already receive our draft specifications please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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**SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/10.379: WHO GOOD MANUFACTURING PRACTICES: WATER FOR PHARMACEUTICAL USE PROPOSAL FOR REVISION**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>The above-mentioned proposal was discussed by the WHO Prequalification Inspection team</td>
<td>January 2010</td>
</tr>
<tr>
<td>Discussion during informal consultation on Quality assurance systems, medicines and risk analysis, Geneva</td>
<td>4-6 May 2010</td>
</tr>
<tr>
<td>Proposed revision mailed out for comments</td>
<td>August 2010</td>
</tr>
<tr>
<td>Collation of comments received</td>
<td>September 2010</td>
</tr>
<tr>
<td>Discussion during 45th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>18-22 October 2010</td>
</tr>
<tr>
<td>Discussion during informal consultation on WHO quality risk management and quality guidelines</td>
<td>28-30 June 2011</td>
</tr>
<tr>
<td>Presentation to the 46th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>10-14 October 2011</td>
</tr>
<tr>
<td>Further action as required</td>
<td></td>
</tr>
</tbody>
</table>
Annex 3

WHO good manufacturing practices: water for pharmaceutical use
Proposal for revision

1. Introduction
   1.1 Scope of the document
   1.2 Background to water requirements and uses
   1.3 Applicable guides
2. General principles for pharmaceutical water systems
3. Water quality specifications
   3.1 General
   3.2 Drinking-water
   3.3 Purified water
   3.4 Highly purified water
   3.5 Water for injections
   3.6 Other grades of water
4. Application of specific waters to processes and dosage forms
5. Water purification systems
   5.1 General considerations
   5.2 Production of drinking-water
   5.3 Production of purified water
   5.4 Production of highly purified water
   5.5 Production of water for injections
6. Water storage and distribution systems
   6.1 General
   6.2 Materials that come into contact with systems for water for pharmaceutical use
   6.3 System sanitization and bioburden control
   6.4 Storage vessel requirements
   6.5 Requirements for water distribution pipework
7. Operational considerations
   7.1 Start-up and commissioning of water systems
   7.2 Qualification
   7.3 Continuous system monitoring
   7.4 Maintenance of water systems
   7.5 System reviews
8. Inspection of water systems

Further reading
1. INTRODUCTION

1.1 Scope of the document

1.1.1 The guidance contained in this document is intended to provide information about the available specifications for water for pharmaceutical use (WPU), guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms, and to provide guidance on good manufacturing practices (GMP) regarding the design, installation and operation of pharmaceutical water systems. Although the focus of this document is on water for pharmaceutical applications, the guidelines may also be relevant to other industrial or specific uses where the specifications and practices can be applied.

*Note:* 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.


1.1.3 This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material.

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

1.1.4 The guidance provided in this document can be used in whole or in part as appropriate to the application under consideration.

1.1.5 Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorization submitted to the national drug regulatory authority.

1.2 Background to water requirements and uses

1.2.1 Water is the most widely used substance, raw material or starting material in the production, processing and formulation of pharmaceutical
products. It has unique chemical properties due to its polarity and hydrogen bonds. This means it is able to dissolve, absorb, adsorb or suspend many different compounds. 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.

1.2.2 Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major concern. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is, therefore, essential. Additionally, certain microbiological tests may require periods of incubation and, therefore, the results are likely to lag behind the water use.

1.2.3 Control of the microbiological quality of WPU is a high priority. Some types of microorganism may proliferate in water treatment components and in the storage and distribution systems. It is very important to minimize microbial contamination by proper design of the system, periodic sanitization and taking appropriate measures to prevent microbial proliferation.

1.2.4 Different grades of water quality are required depending on the route of administration of the pharmaceutical products. One source of guidance about different grades of water is the European Medicines Agency (EMA) Note for guidance on quality of water for pharmaceutical use (CPMP/QWP/158/01). Another reference source is the USP <1231>.

1.3 Applicable guides

1.3.1 In addition to the specific guidance provided in this document, the reference list includes some relevant publications that can serve as additional background material when planning, installing and using systems intended to provide WPU.

2. GENERAL PRINCIPLES FOR PHARMACEUTICAL WATER SYSTEMS

2.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified and maintained to ensure the reliable production of water of an appropriate quality. It is required to validate the water production process on these systems to ensure the water generated, stored and distributed does not exceed the appropriate limits.
2.2 The capacity of the system should be designed to meet the average and the peak flow demand of the current operation. If necessary, depending on planned future demands, the system should be designed to permit increases in the capacity, or designed to permit modification. All systems, regardless of the size and excessive capacity, should have appropriate recirculation and turnover to assure the system is well controlled chemically and microbiologically.

2.3 The use of the systems following installation, commissioning, qualification, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department using change control documentation.

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

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

3. WATER QUALITY SPECIFICATIONS

3.1 General

3.1.1 The following requirements concern water processed, stored and distributed in bulk form. They do not cover the specification of waters formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form waters.

3.1.2 Pharmacopoeial requirements for WPU are described in national, regional and international pharmacopoeias and limits for various impurities or classes of impurities are given. Companies wishing to supply multiple markets should set specifications that meet the strictest requirements from each of the relevant pharmacopoeias.

3.2 Drinking Water

3.2.1 Drinking-water should be supplied under continuous positive pressure in a plumbing system free of any defects that could lead to contamination of any product.
3.2.2 Drinking-water is unmodified except for limited treatment of the water 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 will dictate the treatment required to render it safe for human consumption (drinking). Typical treatment includes desalinization, softening, removal of specific ions, particle reduction and antimicrobial treatment.

3.2.3 It is common for drinking-water to be derived from a public water supply that may be a combination of more than one of the natural sources listed above. It may also be supplied either from an offsite source, e.g. a municipality, or achieved onsite through appropriate processing.

3.2.4 It is also common for public water supply organizations to conduct tests and guarantee that the drinking water delivered is of drinking quality. This testing is typically performed on waters from the water source.

3.2.5 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water treatment system meets the appropriate drinking water requirements. There may be situations where the water treatment system is firstly used to achieve drinking water quality and subsequently purified water. In these situations the point at which drinking water quality is achieved should be identified and tested.

3.2.6 Drinking-water quality is covered by the WHO drinking-water guidelines, 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.

3.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture or is the feed-water 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.

3.3 Purified water

3.3.1 Purified water (PW) should be prepared from a drinking-water source as a minimum-quality feed-water. It should meet the relevant pharmacopoeial specifications for chemical, and microbiological purity with appropriate action and alert limits. It should also be protected from recontamination and microbial proliferation.

3.4 Highly purified water

3.4.1 Highly purified water (HPW) should be prepared from drinking-water as a minimum-quality feed-water. HPW is a unique specification for water found only in the European Pharmacopoeia. This grade of water must meet the same quality
standard as water for injections (WFI) including the limit for endotoxins, but the water-
treatment process used may be different. The HPW process system may include
appropriate methods other than distillation. HPW may be prepared by a combination
of methods which may include ion exchange, reverse osmosis, electrodeionization,
ultrafiltration and/or distillation.

3.4.2 HPW should also be protected from recontamination and microbial proliferation.

3.4.3 HPW and WFI have the identical stringent microbiological requirements.

3.5 Water for injections

3.5.1 Water for injections (WFI) should be prepared from drinking-water (usually with
further treatment) or purified water as a minimum-quality feed-water WFI is not sterile
water and is not a final dosage form. It is an intermediate bulk product and suitable to
be used as an ingredient during formulation. WFI is the highest quality of
pharmacopoeial WPU.

3.5.2 Certain pharmacopoeias place constraints upon the permitted purification
techniques as part of the specification of the WFI. The International
Pharmacopoeia and the European Pharmacopoeia, for example, allow only distillation as the final purification step.

3.5.3 WFI should meet the relevant pharmacopoeial specifications for chemical and
microbiological purity (including endotoxin) with appropriate action and alert limits.

3.5.4 WFI should also be protected from recontamination and microbial proliferation.

3.6 Other grades of water

3.6.1 When a specific process requires a special non-pharmacopoeial grade of water,
its specification must be documented within the company 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.

4. APPLICATION OF SPECIFIC WATERS TO PROCESSES AND DOSAGE
FORMS

4.1 Product licensing authorities specify the minimum grade of WPU that must be
used during the manufacture of the different dosage forms or for different stages in
washing, preparation, synthesis, manufacturing or formulation.

4.2 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.
4.3 HPW 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 pharmacopoeial monographs for WFI.

4.4 WFI should be used in the manufacture of injectable products for dissolving or diluting substances or preparations during the manufacture of parenterals for administration before use, and for manufacture of sterile water for preparation of injections. WFI should also be used for the final rinse after 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.

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

5. WATER PURIFICATION SYSTEMS

5.1 General considerations

5.1.1 The specifications for WPU found in compendia (e.g. pharmacopoeias) do not define the permissible water purification methods apart from WFI (refer to section 3.5).

5.1.2 The chosen water purification method, or sequence of purification steps, must be appropriate to the application in question. The following should be considered when selecting the water treatment method:

— the final water quality specification;
— the quantity of water required by the user;
— the available feed-water quality and the variation over time (seasonal changes);
— the availability of suitable support facilities for system connection (raw water, electricity, heating steam, chilled water, compressed air, sewage system, exhaust air);
— 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, days/years and planned downtime; and
— the total life-cycle costs (capital and operational including maintenance).
5.1.3 The specifications for water purification equipment, storage and distribution systems should take into account the following:

— the risk of contamination from leachates from contact materials;
— the adverse impact of adsorptive contact materials;
— hygienic or sanitary design, where required;
— corrosion resistance;
— freedom from leakage;
— a system configuration to avoid proliferation of microbiological organisms.
— tolerance to cleaning and sanitizing agents (thermal and/or chemical);
— the sanitation strategy
— the system capacity and output requirements; and
— the provision of all necessary instruments, test and sampling points to allow all the relevant critical quality parameters of the complete system to be monitored.

5.1.4 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

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

5.2 Production of drinking-water

5.2.1 Drinking-water is derived from a raw water source such as a well, river or reservoir. There are no prescribed methods for the treatment of raw water to produce drinking-water from a specific raw water source.

5.2.2 Typical processes employed at a user plant or by a water supply authority include:

— desalination;
— filtration;
— softening;
— disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
— iron (ferrous) removal;
— precipitation; and
— reduction of concentration of specific inorganic/organic materials.
5.2.3 The drinking-water quality should be monitored routinely to account for environmental, seasonal or supply changes impacting the source water quality.

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

5.2.5 Trend review may be used to identify 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 feed-water to downstream treatment stages, should be reviewed and the result of the review documented.

5.2.6 Where drinking-water is derived from an “in-house” system for the treatment of raw water, the water-treatment steps used and the system configuration should be documented. Changes to the system or its operation should not be made until a review has been completed and the change approved by the QA department in accordance with change control procedures.

5.2.7 Where drinking-water is stored and distributed by the user, the storage systems must not allow degradation of the water quality before use. After any such storage, testing should be carried out routinely in accordance with a defined method. Where water is stored, the system design and operation should ensure a turnover or recirculation of the stored water sufficient to prevent stagnation.

The drinking-water system is usually considered to be an “indirect impact system” and does not need to be qualified.

5.2.8 Drinking-water purchased in bulk and transported to the user by tanker has additional problems and risks not associated with drinking-water delivered by pipeline. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

5.2.9 Equipment and systems used to produce drinking-water should be able to be drained and sanitized. Storage tanks should be closed with appropriately protected vents, allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained or flushed and sanitized.

5.2.10 Special care should be taken to control microbiological contamination of sand filters, carbon beds and water softeners. Once microorganisms have infected a system, the contamination can rapidly form biofilms and spread throughout the system. Techniques for controlling contamination such as back-flushing, chemical and/or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be flushed periodically with water at a flow rate that is sufficient to prevent microbial proliferation.
5.3 Production of purified water

5.3.1 Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Purified water is commonly produced by ion exchange, reverse osmosis, ultrafiltration and/or electro-deionization processes and distillation.

5.3.2 The following should be considered when configuring a water purification system:

— the feed-water quality and its variation over seasons;
— the quantity of water required by the user;
— the required water-quality specification;
— the sequence of purification stages required;
— the energy consumption;
— the extent of pretreatment required to protect the final purification steps;
— performance optimization, including yield and efficiency of unit treatment-process steps;
— appropriately located sampling points designed in such a way as to avoid potential contamination; and
— unit process steps should be provided with appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity, pH and total organic carbon.

5.3.3 Ambient-temperature systems such as ion exchange, reverse osmosis and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. It is essential to consider the mechanisms for microbiological control and sanitization.

5.3.4 The following techniques should be considered:

— maintenance of minimum flow through the water generation system is recommended at all times;
— control of temperature in the system by heat exchanger or plant-room cooling to reduce the risk of microbial growth (guidance value <25 °C);
— provision of ultraviolet disinfection;
— selection of water-treatment components that can be periodically thermally sanitized; and/or
— application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid).

5.4 Production of highly purified water

5.4.1 Highly purified water can be produced by double-pass reverse osmosis coupled with ultrafiltration, or by distillation or by any other appropriate qualified purification technique or sequence of techniques.
5.4.2 The guidance provided in section 5.3 for PW is equally applicable to HPW.

5.5 **Production of water for injection(s)**

5.5.1 Some pharmacopoeias prescribe or limit the permitted final water purification stage in the production of WFI. Distillation is the preferred technique; it is considered a more robust technique based on phase change, and in some cases, high temperature operation of the process equipment.

5.5.2 The following should be considered when designing a water purification system:

- the feed-water quality;
- the required water quality specification;
- the quantity of water;
- 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.

5.5.3 The system configuration guidance provided in section 5.3 for PW is equally applicable to water for injection.

6. **WATER STORAGE AND DISTRIBUTION SYSTEMS**

6.1 This section applies to WPU systems for PW, HPW and WFI. The water storage and distribution should work in conjunction with the purification plant to ensure delivery of consistent quality water to the user points, and to ensure optimum operation of the water purification equipment.

6.1 **General**

6.1.1 The storage and distribution system should be considered as a key part of the whole system, and should be designed to be fully integrated with the water purification components of the system.

6.1.2 Once water has been purified using an appropriate method, it can either be used directly or, more frequently, it will be fed into a storage vessel for subsequent distribution to points of use. The following text describes the requirements for storage and distribution systems.

6.1.3 The storage and distribution system should be configured to prevent microbial proliferation and recontamination of the water (PW, HPW, WFI) after treatment. It should be subjected to a combination of online and offline monitoring to ensure that the appropriate water specification is maintained.
6.2 **Materials that come into contact with systems for water for pharmaceutical use**

6.2.1 This section applies to generation equipment for PW, HPW and WFI and the associated storage and distribution systems.

6.2.2 The materials that come into contact with WPU, including pipework, valves and fittings, seals, diaphragms and instruments, should be selected to satisfy the following objectives.

- **Compatibility.** The compatibility and suitability of the materials should encompass the full range of its working temperature and potential chemicals that it will come into contact with the system at rest, in operation and during sanitization.

- **Prevention of leaching.** All materials that come into contact with WPU should be non-leaching at the range of working and sanitization temperatures of the system.

- **Corrosion resistance.** PW, HPW and WFI are highly corrosive. To prevent failure of the system and contamination of the water, the materials selected must be appropriate, the method of jointing must be carefully controlled, and all fittings and components must be compatible with the pipework used. Appropriate sanitary specification plastics and stainless steel materials are acceptable for WPU systems. When stainless steel is used it should be at least grade 316L. The system should be passivated after initial installation or after significant modification. When accelerated passivation is undertaken, the system should be thoroughly cleaned first, and the passivation process should be undertaken in accordance with a clearly defined documented procedure.

- **Smooth internal finish.** Once water has been purified it is susceptible to microbiological contamination, and the system is subject to the formation of biofilms when cold storage and distribution is employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices are frequently sites where corrosion can commence. The internal material finish should have an arithmetical average surface roughness of not greater than 0.8 micrometer (Ra). When stainless steel is used, mechanical and electro-polishing techniques may be employed. Electro-polishing improves the resistance of the stainless steel material to surface corrosion.

- **Jointing.** The selected system materials should be easily joined by welding in a controlled manner. The control of the process should include as a minimum, qualification of the operator, documentation of the welder set-up, work session test pieces (coupons), logs of all welds and visual inspection of a defined proportions of welds, e.g. 100% hand welds, 10% automatic welds.
• *Design of flanges, unions and valves.* Where flanges, unions or valves are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly. Threaded connections should be avoided.

• *Documentation.* All system components should be fully documented and be supported by original or certified copies of material certificates.

• *Materials.* Suitable materials that may be considered for sanitary elements of the system include 316 L (low carbon) stainless steel, polypropylene, polyvinylidenedifluoride and perfluoroalkoxy. The choice of material should take into account the intended sanitization method. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

### 6.3 System sanitization and bioburden control

6.3.1 Water treatment equipment, storage and distribution systems used for PW, HPW and WFI should be provided with features to control the proliferation of microbiological organisms during normal use, as well as techniques for sanitizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and should account for the interdependency between the materials and the sanitization techniques.

6.3.2 Systems that operate and are maintained at elevated temperatures (e.g. >65 to 80 °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, then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.5.3 for guidance).

### 6.4 Storage vessel requirements

6.4.1 General

6.4.1.1 The water storage vessel used in a system serves a number of important functions. The design and size of the vessel should take into consideration the following.

6.4.2 Capacity

6.4.2.1 The capacity of the storage vessel should be determined on the basis of the following requirements:
• it is necessary to provide a buffer capacity between the steady-state generation rate of the water-treatment equipment and the potentially variable simultaneous demand from user points;

• the water treatment equipment should be able to operate continuously for significant periods to avoid the inefficiencies and equipment stress that occur when the equipment cycles on and off too frequently; and

• the capacity should be sufficient to provide short-term reserve capacity in the event of failure of the water-treatment equipment or inability to produce water due to a sanitization or regeneration cycle. When determining the size of such reserve capacity, consideration should be given to providing sufficient water to complete a process batch, work session, tank turnover by recirculation to minimize stagnation or other logical period of demand.

6.4.3 Contamination control considerations

6.4.3.1 The following should be taken into account for the efficient control of contamination:

• the headspace in the storage vessel is an area of risk where water droplets and air can come into contact at temperatures that encourage the proliferation of microbiological organisms. The use of spray-ball or distributor devices should be considered in these systems to wet the surfaces during normal operation, chemical and/or thermal sanitization. If ozone is used as a continuous sanitizing agent in the tank the use of a spray ball is not recommended;

• nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harboured;

• vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should be bacteria-retentive, hydrophobic and ideally be configured to allow in situ testing of integrity. Offline testing is also acceptable. The use of heated vent filters should be considered for continuous hot storage or systems using periodic heat sanitization to prevent condensation within the filter matrix that might lead to filter blockage and to microbial growth that could contaminate the storage vessels; and

• where pressure-relief valves and bursting discs are provided on storage vessels to protect them from under- and over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to ensure that loss of system integrity is detected.
6.5 **Requirements for water distribution pipework**

6.5.1 **General**

6.5.1.1 The distribution of PW, HPW and WFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within the storage tank and distribution loop should be controlled. Good cause for utilizing a non-recirculating one-way system should be rationalized.

6.5.1.2 Filtration should not usually be used in distribution loops or at takeoff user points to control biocontamination. Such filters are likely to conceal system contamination.

6.5.2 **Temperature control and heat exchangers**

6.5.2.1 Where heat exchangers are employed to heat or cool WPU within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water. The more secure types of heat exchangers of the double tube plate or 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 is not usually practiced in WFI systems.

6.5.2.2 Where heat exchangers are used they should be arranged in continually circulating loops or subloops of the system to avoid unacceptable static water in systems.

6.5.2.3 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.

6.5.3 **Circulation pumps**

6.5.3.1 Circulation pumps should be of a sanitary design with appropriate seals that prevent contamination of the system. Where stand-by pumps are provided, they should be configured or managed to avoid dead zones trapped within the system.

6.5.4 **Biocontamination control techniques**

6.5.4.1 The following control techniques may be used alone or more commonly in combination:
• maintenance of continuous turbulent flow circulation within water distribution systems reduces the propensity for the formation of biofilms. The Reynolds Value\(^1\) should be used to determine the required design velocity. The maintenance of the design velocity for a specific system should be proven during the system qualification and the maintenance of satisfactory performance should be monitored. During the operation of a distribution system, short-term fluctuations in the flow velocity are unlikely to cause contamination problems provided that cessation of flow, flow reversal or pressure loss does not occur;

• the system design should ensure the shortest possible length of pipework;

• for ambient temperature systems, pipework should be isolated from adjacent hot pipes;

• deadlegs in the pipework should be minimized through appropriate design, and as a guide should not significantly exceed three times the branch diameter as measured from the ID pipewall to centerline of the point of use valve, where significant stagnation potential exists;

• pressure gauges should be separated from the system by membranes;

• hygienic pattern diaphragm valves should be used;

• pipework for steam-sanitized systems should be sloped and fully drainable;

• the growth of microorganisms can be inhibited by:
  — ultraviolet radiation sources in pipework;
  — maintaining the system heated (greater than 65 °C);
  — sanitizing the system periodically using hot water (guidance temperature >70 °C);
  — sanitizing the system periodically using superheated hot water or clean steam; or
  — routine chemical sanitization using ozone or other suitable chemical agents. When chemical sanitization is used, it is essential to prove that the agent has been removed prior to using the water. Ozone can be effectively removed by using ultraviolet radiation.

\[ R = \frac{\rho V D}{\mu} \]

\( R \): Reynolds number.

\( V \): Free-stream fluid velocity.

\( D \): Characteristic distance (or pipe diameter).

\( \rho \): Fluid density.

\( \mu \): Fluid viscosity (dynamic).
7. OPERATIONAL CONSIDERATIONS

7.1 Start-up and commissioning of water systems

7.1.1 Planned, well-defined, successful and well-documented commissioning and qualification is an essential precursor to successful validation of water systems.

7.1.2 The commissioning work should include setting to work, system set-up, controls loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

7.2 Qualification

7.2.1 WPU, PW, HPW and WFI systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

7.2.2 This guidance does not define the standard requirements for the conventional qualification stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Phase 1. A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following should be included in the testing approach. Usually water is not used for finished pharmaceutical product (FPP) manufacturing during this period.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample or continuously monitor the incoming feed-water daily to verify its quality.
- Sample or continuously monitor after each step in the purification process.
- Sample or continuously monitor at each point of use and at other defined sample points.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate 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.
- Develop and refine test-failure procedure.
Phase 2. A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Use of the water for FPP manufacturing purposes during this phase may be acceptable, provided that both commissioning and Phase 1 data demonstrate 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.

Phase 3. Phase 3 typically runs for 1 year after the satisfactory completion of phase 2. Water can be used for FFP manufacturing purposes during this phase which has the following objectives and features.

• Demonstrate extended reliable performance.
• Ensure that seasonal variations are evaluated.
• The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

7.3 Continuous system monitoring

7.3.1 After completion of phase 3 of the qualification programme for the WPU system, a system review should be undertaken. Following this review, a routine monitoring plan should be established based on the results of phase 3.

Monitoring should include a combination of online instrument monitoring of parameters such as flow, pressure, temperature, conductivity and total organic carbon, and offline sample testing for physical, chemical and microbiological attributes. Offline samples should be taken from points of use or dedicated sample points where points of use cannot be sampled. During validation water samples should be taken using the same methodology as detailed in production procedures. There should be an applicable flushing and drainage procedure in place.

7.3.2 Tests should be carried out to ensure that the approved specification, pharmacopeial and company specification has been met. The specification should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, oxidizable substances, total viable count, presence of specific pathogens and endotoxins (for WFI only). Monitoring data should be subject to trend analysis.

7.3.3 Any trend towards frequently exceeding alert limits should trigger a thorough investigation of the root cause, followed by appropriate corrective actions.
7.4 **Maintenance of water systems**

7.4.1 WPU systems should be maintained in accordance with a controlled, documented maintenance programme that takes into account the following:

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

7.5 **System reviews**

7.5.1 WPU (PW, HPW and WFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, operations and maintenance. The review should consider matters such as:

- changes made since the last review;
- system performance;
- reliability;
- quality trends;
- failure events;
- investigations;
- out-of-specifications results from monitoring;
- changes to the installation;
- updated installation documentation;
- log books; and
- the status of the current standard operating procedures (SOP) list.

7.5.2 For new systems, or systems that display instability or unreliability, the following should also be reviewed:

- need for investigation;
- corrective actions and preventative actions CAPA; and
- qualification (DQ, IQ, OQ, PQ or equivalent verification documents) and monitoring phases of the system.

8. **INSPECTION OF WATER SYSTEMS**

8.1 WPU (PW, HPW and WFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audit and self-inspection of established water systems.
8.2 This GMP guidance can be used as the basis of inspection. The following list identifies items and a logical sequence for a WPU system inspection or audit:

— a current drawing of the water system showing all equipment in the system from the inlet to the points of use along with sampling points and their designations;
— approved piping drawings (e.g., orthographic and/or isometric);
— a sampling and monitoring plan with a drawing of all sample points;
— training programme for sample collection and testing;
— the setting of monitoring alert and action levels;
— monitoring results and evaluation of trends;
— inspection of the last annual system review;
— review of any changes made to the system since the last audit and check that the change control has been implemented;
— review of deviations recorded and their investigation;
— general inspection of system for status and condition;
— review of maintenance, failure and repair logs; and
— checking calibration and standardization of critical instruments.

8.3 For an established system that is demonstrably under control, this scope of review should prove adequate.

Further reading


Baines PH. Passivation; understanding and performing procedures on austenitic stainless steel systems. Pharmaceutical Engineering, 1990, 10(6).


European Pharmacopoeia: web site for the publishers of the European Pharmacopoeia and supplements; http://www.pheur.org/.


US Pharmacopoeia: Published annually; see http://www.usp.org/

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