



ANNEX 5: WATER FOR PHARMACEUTICAL USE

1.1 Scope

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 the good manufacturing practice (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.

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.

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

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.



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1.2 Background to water requirements and uses

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.

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).

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. 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 routine sanitization and taking appropriate measures to prevent microbial proliferation.



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1.3 Applicable guides

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

2. General Requirements for Pharmaceutical Water Systems

Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, validated and maintained to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner that prevents unacceptable microbial, chemical or physical contamination (e.g. with dust and dirt).

The use of the systems following installation, commissioning, validation and any unplanned maintenance or modification work should be approved by the quality assurance (QA) department. If approval is obtained for planned preventive maintenance tasks, they need not be approved after implementation. Water sources and treated water should be monitored regularly for quality and 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 and any actions taken should be maintained for an appropriate length of time.

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



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3. Water quality specifications

3.1 General

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.

Pharmacopoeial requirements for WPU are described in national and international pharmacopoeias and limits for various contaminants 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

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.

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 softening, removal of specific ions, particle reduction and antimicrobial treatment. 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 is also common for public water-supply organizations to conduct tests and guarantee that the drinking-water delivered is of potable quality.

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.



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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 potable water.

3.3 Purified water

Purified water (PW) should be prepared from a potable water source as a minimum-quality feed-water, should meet the pharmacopoeial specifications for chemical and microbiological purity, and should be protected from recontamination and microbial proliferation.

3.4 Highly purified water

Highly purified water (HPW) should be prepared from potable water as 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 methods are not considered to be as reliable as distillation. HPW may be prepared by combinations of methods such as reverse osmosis, ultra filtration and deionization.

3.5 Water for injections

Water for injections (WFI) should be prepared from potable 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. WFI is the highest quality of pharmacopoeial WPU.

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.



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3.6 Other grades of water

When a specific process requires a special non-pharmacopoeial grade of water, this should be specified and should at least satisfy the pharmacopoeial requirements of the grade of WPU required for the type of dosage form or process step.

4. Application of specific waters to processes and dosage forms

Product licensing authorities define the requirement to use the specific grades of WPU for different dosage forms or for different stages in washing, preparation, synthesis, manufacturing or formulation.

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.

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.

WFI should be used in injectable product preparations, for dissolving or diluting substances or preparations for parenteral administration before use, and for 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.

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



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5. Water purification methods

5.1 General considerations

The specifications for WPU found in compendia (e.g. pharmacopoeias) are generally not prescriptive as to permissible water purification methods other than those for WFI (refer to section 3.5).

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 water quality specification;
- the yield or efficiency of the purification system;
- feed-water quality and the variation over time (seasonal changes);
- the reliability and robustness of the water-treatment equipment in operation;
- the availability of water-treatment equipment on the market;
- the ability to adequately support and maintain the water purification equipment; and
- the operation costs.

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;
- configuration to avoid proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and chemical);
- 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



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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 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

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 potable drinking-water from a specific raw water source.

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

- filtration;
- softening;
- disinfection or sanitization (e.g. by sodium hypochlorite (chlorine) injection);
- iron (ferrous) removal;
- precipitation; and
- reduction of specific inorganic/organic materials.

The drinking-water quality should be monitored routinely. Additional testing should be considered if there is any change in the raw-water source, treatment techniques or system configuration. If the drinking water quality changes significantly, 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.



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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.

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, its use should ensure a turnover 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.

Drinking-water purchased in bulk and transported to the user by tanker presents special problems and risks not associated with potable 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.

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 pipe work should be able to be drained, or flushed, and sanitized.

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 or thermal sanitization and frequent regeneration should be considered. Additionally, all water-treatment components should be maintained with continuous water flow to inhibit microbial growth.



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5.3 Production of purified water

There are no prescribed methods for the production of PW in the pharmacopoeias. Any appropriate qualified purification technique or sequence of techniques may be used to prepare PW. Typically ion exchange, ultra filtration and/or reverse osmosis processes are used. Distillation can also be used.

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

- the feed-water quality and its variation over seasons;
- 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.

Ambient-temperature PW systems 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. The following techniques should be considered:

- maintenance of flow through water-purification equipment at all times;
- control of temperature in the system by pipeline heat exchange or plant-room cooling to reduce the risk of microbial growth (guidance value <math><25^{\circ}\text{C}</math>);
- provision of ultraviolet disinfection;
- selection of water-treatment components that can be thermally sanitized; and/or
- application of chemical sanitization (including agents such as ozone).



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5.4 Production of highly purified water

There are no prescribed methods for the production of HPW in any major pharmacopoeia, including the European Pharmacopoeia. Any appropriate qualified purification technique or sequence of techniques may be used to prepare HPW. Typically ion exchange, ultrafiltration and/or reverse osmosis processes are used. The guidance provided in section 5.3 for PW is equally applicable to HPW.

5.5 Production of water for injections

The 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.

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

- the feed-water quality;
- the required water quality specification;
- the optimum generator size to avoid over-frequent start/stop cycling;
- blow-down and dump functions; and
- cool-down venting to avoid contamination ingress.

6. Water purification, storage and distribution systems

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 consistent delivery of water to the user points, and to ensure optimum operation of the water purification equipment.



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6.1 General

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.

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.

The storage and distribution system should be configured to prevent recontamination of the water after treatment and 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

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

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

- **Compatibility.** All materials used should be compatible with the temperature and chemicals used by or in the system.
- **Prevention of leaching.** All materials that come into contact with WPU should be non-leaching at the range of working temperatures.
- **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 pipe work 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 316 L. The system should be passivated after initial installation or



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after 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 finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre arithmetical mean roughness (Ra). When stainless steel is used, mechanical and electropolishing techniques may be employed. Electropolishing improves the resistance of the stainless-steel material to surface corrosion.
- Jointing. The selected system materials should be able to be easily jointed 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, logs of all welds and visual inspection of a defined proportions of welds.
- Design of flanges or unions. Where flanges or unions are used, they should be of a hygienic or sanitary design. Appropriate checks should be carried out to ensure that the correct seals 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 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. Other materials such as unplasticized polyvinylchloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.



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6.3 System sanitization and bioburden control

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 or sterilizing the system after intervention for maintenance or modification. The techniques employed should be considered during the design of the system and their performance proven during the commissioning and qualification activities.

Systems that operate and are maintained at elevated temperatures, in the range of 70–80°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

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

6.4.1 Capacity

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



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- 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.
- 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 or other logical period of demand.

6.4.2 Contamination control considerations

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 water distribution loop should be configured to ensure that the headspace of the storage vessel is effectively wetted by a flow of water. The use of spray ball or distributor devices to wet the surfaces should be considered.
- Nozzles within the storage vessels should be configured to avoid dead zones where microbiological contamination might be harbored.
- 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 to prevent condensation within the filter matrix that might lead to filter blockage and to microbial grow-through that could contaminate the storage vessels.
- Where pressure-relief valves and bursting discs are provided on storage vessels to protect them from over-pressurization, these devices should be of a sanitary design. Bursting discs should be provided with external rupture indicators to prevent accidental loss of system integrity.



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6.5 Requirements for water distribution pipework

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.

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.

6.5.1 Temperature control and heat exchangers

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 configuration should be considered. Where these types are not used, an alternative approach whereby the utility is main-trained and monitored at a lower pressure than the WPU may be considered. Where heat exchangers are used they should be arranged in continually circulating loops or sub-loops of the system to avoid unacceptable static water in systems.

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.

6.5.2 Circulation pumps

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.



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6.5.3 Biocontamination control techniques

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 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 installation greater than 1.5 times the branch diameter should be avoided.
- Pressure gauges should be separated from the system by membranes.
- Hygienic pattern diaphragm valves should be used.
- Pipework should be laid to falls to allow drainage.
- The growth of microorganisms can be inhibited by:
 1. ultraviolet radiation sources in pipework;
 2. maintaining the system heated (guidance temperature 70–80°C);
 3. sanitizing the system periodically using hot water (guidance temperature >70°C);
 4. sterilizing or sanitizing the system periodically using superheated hot water or clean steam; and
 5. 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.



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7. Operational considerations

7.1 Start-up and commissioning of water systems

Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system setup, 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

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).

This guidance does not define the standard requirements for the conventional validation 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.

Phase1: 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.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample the incoming feed-water daily to verify its quality.



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- Sample after each step in the purification process daily.
- Sample at each point of use and at other defined sample points daily.
- 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 and action 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. Water can be used for manufacturing purposes during this phase. 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 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.



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7.3 Continuous system monitoring

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 and specific sample points. Samples from points of use should be taken in a similar way to that adopted when the water is being used in service.

Tests should be carried out to ensure that the selected pharmacopoeia specification has been satisfied, and should include, as appropriate, determination of conductivity, pH, heavy metals, nitrates, total organic carbon, total viable count, presence of specific pathogens and endotoxins.

Monitoring data should be subject to trend analysis.

7.4 Maintenance of water systems

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.



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7.5 System reviews

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 SOP list.