Annex 2

WHO good manufacturing practices: water for pharmaceutical use[1]

1 The current document is a revision of WHO good manufacturing practices: water for pharmaceutical use, previously published in WHO Technical Report Series, No. 929, Annex 3, 2005.

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.

1.1.2 The GMP guidance for WPU contained in this document is intended to be supplementary to the general GMP guidelines for pharmaceutical products published by WHO (*WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908), Annex 4).

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.

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 medicines 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 crucial to minimize microbial contamination by proper design of the system, periodic sanitization and by 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. Other sources of guidance about different grades of water can be found in pharmacopoeias and related documents.

1.3 Applicable guides

1.3.1 In addition to the specific guidance provided in this document, the Further reading section 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 necessary to validate the water production process to ensure the water generated, stored and distributed is not beyond the designed capacity and meets its specifications.

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 their size and 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 initial validation (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) and after any planned and 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 ensure 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 water formulated for patient administration. Pharmacopoeias include specifications for both bulk and dosage-form types of water.

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

Similarly, requirements or guidance are given in pharmacopoeias on the microbiological quality of water.

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 appropriate quality may be 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 water 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 (PW) treatment system meets the appropriate drinking-water requirements. There may be situations where the water treatment system is used first 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 Bulk purified water

3.3.1 Bulk purified water (BPW) 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. BPW may be prepared by a combination of reverse osmosis (RO) RO/electro-deionization (EDI) and vapour compression (VC). Alert levels for the water system should be determined from knowledge of the system and are not specified in the pharmacopoeias.

3.4 Bulk highly purified water

3.4.1 Bulk highly purified water (BHPW) should be prepared from drinking-water as a minimum-quality feed-water. BHPW 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. Current production methods include, for example, double-pass RO coupled with other suitable techniques such as ultrafiltration and deionization.

BHPW may be prepared by a combination of different methods such as RO, ultrafiltration and deionization.

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

3.4.3 BHPW and WFI have identical microbiological requirements.

3.5 Bulk water for injections

3.5.1 Bulk water for injections (BWFI) should be prepared from drinking-water (usually with further treatment) or purified water as a minimum-quality feed-water. BWFI 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. BWFI 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 BWFI. *The International Pharmacopoeia* and the *European Pharmacopoeia*, for example, allow only distillation as the final purification step.

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

3.5.4 BWFI 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 types of water 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 BHPW can be used in the preparation of products when water of high quality (i.e. very low in microorganisms and endotoxins) is needed, but the

process stage or product requirement does not include the constraint on the production method defined in some of the pharmacopoeial monographs for BWFI.

4.4 BWFI should be used in the manufacture of injectable products for dissolving or diluting substances or preparations during the manufacturing of parenterals, and for manufacture of sterile water for preparation of injections. BWFI 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 with equipment for preparing injectable products, it should conform to the specification for BWFI 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 for BWFI (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;
- 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 location of the plant room;
- extremes in temperature that the system will encounter;
- 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 sanitization strategy;
- the system capacity and output requirements;
- 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;
- 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:

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

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

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

5.2.9 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.

5.2.10 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, and should allow for visual inspection and for being drained and sanitized. Distribution pipework should be able to be drained or flushed and sanitized.

5.2.11 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 as appropriate.

5.3 Production of purified water

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

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

- 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;
- 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, RO 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.

The method for sanitizing each stage of purification needs to be defined and must include verification of the removal of any agents used. There should be documented evidence of its efficacy.

5.3.4 The following 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 periodically be thermally sanitized;
- application of chemical sanitization (including agents such as ozone, hydrogen peroxide and/or peracetic acid);
- thermal sanitization at > 65 °C.

5.4 Production of highly purified water

5.4.1 Highly purified water (HPW) can be produced by double-pass reverse osmosis coupled with ultrafiltration 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 BWFI. 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 and defining URS:

- 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;
- 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, BHPW and BWFI. The water storage and distribution should work in conjunction with the purification plant to ensure delivery of water of consistent quality 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 and point of use (POU).

6.1.3 The storage and distribution system should be configured to prevent microbial proliferation and recontamination of the water (PW, BHPW, BWFI) 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, BHPW and BWFI 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 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, BHPW and BWFI 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 316. In general 316L or a higher grade of stainless steel is used.

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 are employed. Smooth internal surfaces help to avoid roughness and crevices within the WPU system. Crevices can be the source of contamination because of possible accumulation of microorganisms and formation of biofilms. Crevices are also frequently sites where corrosion can commence. The internal material finish should have an arithmetical average surface roughness of not greater than 0.8 micrometre (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 proportion 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 316L (low carbon) stainless steel, polypropylene, polyvinylidene-difluoride and perfluoroalkoxy. The choice of material should take into account the intended sanitization method. Other materials such as unplasticized polyvinyl-chloride (uPVC) may be used for treatment equipment designed for less pure water such as ion exchangers and softeners.

None of the materials that come into contact with WPU should contain chemicals that will be extracted by the water. Plastics should be non-toxic and should be compatible with all chemicals used. They should be manufactured from materials that should at least meet minimum food grade standards. Their chemical and biological characteristics should meet any relevant pharmacopoeia specifications or recommendations.

Precautions should be taken to define operational limits for areas where water circulation is reduced and turbulent flow cannot be achieved. Minimum flow rate and change volumes should be defined.

6.3 System sanitization and bioburden control

6.3.1 Water treatment equipment, storage and distribution systems used for BPW, BHPW and BWFI 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 take into account the interdependency between the materials and the sanitization techniques.

6.3.2 Systems that operate and are maintained at elevated temperatures (e.g. > 65) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants (see section 6.4.3 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.

- 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.
- 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 should 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.
- 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 BPW, BHPW and BWFI should be accomplished using a continuously circulating pipework loop. Proliferation of contaminants within

the storage tank and distribution loop should be controlled. Good justification for using a non-recirculating one-way system should be provided.

6.5.1.2 Filtration should not usually be used in distribution loops or at take off-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 approach is not usually adopted in BWFI 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.

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

6.5.4 Biocontamination control techniques

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

6.5.4.2 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 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 pipe wall to centre line 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;
  - 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.

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 to 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, BPW, BHPW and BWFI 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), IQ, OQ, and 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.

Tests on the source water must be included within the validation programme and continued as part of the routine monitoring. The source water should meet the requirements for drinking-water and any internal specification.

Phase 1. Sample daily or continuously monitor the incoming feed-water to verify its quality.

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

- 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 two 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;
- 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 one year after the satisfactory completion of phase 2. Water can be used for FFP manufacturing purposes during this phase which has the following objectives:

- to demonstrate reliable performance over an extended period;
- to 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 monitoring with online instruments (with appropriately qualified alarm systems) 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. All water samples should be taken using the same methodology as detailed in production procedures. There should be a suitable flushing and drainage procedure in place.

7.3.2 Tests should be carried out to ensure that the approved pharmacopoeial and company specification has been met.

This may include the microbiological quality of water as appropriate.

Monitoring data should be subject to trend analysis (trending should typically be within 2 sigma). Suitable alert and action levels should be established based on historical reported data.

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 a clear maintenance plan and instructions;
- review and approval of systems for use upon completion of work;
- record and review of problems and faults during maintenance.

7.5 System reviews

7.5.1 WPU (BPW, BHPW and BWFI) systems should be reviewed at appropriate regular intervals. The review team should comprise representatives from engineering, QA, microbiology, 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;
- the status of the current 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);

– qualification (DQ, factory acceptance test (FAT), IQ, site acceptance test (SAT), OQ, PQ) or equivalent verification documents, and monitoring phases of the system.

8. Inspection of water systems

8.1 WPU (BPW, BHPW and BWFI) systems are likely to be the subject of regulatory inspection from time to time. Users should consider conducting routine audit and self-inspection of established water systems.

8.2 This GMP guidance can be used as the basis of inspection. A tour of the water generation plant and visible pipework (including user points) should be performed to ensure that the system is appropriately designed, installed and maintained (e.g. that there are no leaks and that the system matches the piping and instrumentation diagram or drawing (P&ID).

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 a 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;
– 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

The International Pharmacopoeia. Geneva, World Health Organization; http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html.

WHO guidelines on good manufacturing practices: validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937); http://www.who.int/medicines/publications/pharmprep/TRS_937.pdf#page=119.

WHO Guidelines for drinking-water quality, 3rd edition. Geneva, World Health Organization, 2008; http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html.

American Society of Mechanical Engineers. *Bioprocessing Equipment Standard*. ASME — BPE 2000.

Banes PH. Passivation; understanding and performing procedures on austenitic stainless steel systems. *Pharmaceutical Engineering*, 1990: 41.

Guide to inspections of high purity water systems. Maryland, US Food and Drug Administration, 1993; http://www.fda.gov/ICECI/InspectionGuides.

Biotechnology. Equipment. Guidance on testing procedures for cleanability. British Standards Publishing. BS EN 12296, 1998.

European Medicines Agency. *Note for guidance on the quality of water for pharmaceutical use*. London, 2002 (CPMP/QWP/158-01); http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003394.pdf.

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

Harfst WH. Selecting piping materials for high-purity water systems. *Ultra Pure Water*, May/June 1994.

ISPE Good practice guide: commissioning and qualification of pharmaceutical water and steam systems. ISPE Baseline TM Pharmaceutical Engineering Guide, Vol. 4. International Society for Pharmaceutical Engineering, 2007.

ISPE Baseline Guide Volume 4: Water and Steam Systems. International Society for Pharmaceutical Engineering, 2001.

Noble PT. Transport considerations for microbial control in piping. *Journal of Pharmaceutical Science and Technology*, 1994, 48: 76–85.

Pharmaceutical Inspection Co-operation Scheme. *PIC/S; Inspection of utilities; P1 009-1*. Geneva, Pharmaceutical Inspection Co-operation Scheme, 2002.

Tverberg JC, Kerber SJ. Effect of nitric acid passivation on the surface composition of mechanically polished type 316 L sanitary tube. *European Journal of Parenteral Sciences,* 1998, 3: 117–124.

US Food and Drug Administration. *Guide to inspections of high purity water systems, high purity water systems* (7/93), 2009; http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074905.htm.

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