WATER SYSTEMS FOR MANUFACTURERS OF NON-STERILE PRODUCTS
1. INTRODUCTION

1.1 This document provides guidance on the essential requirements for water purification systems, which are installed for the production of water used in the manufacture of non-sterile products. It must be emphasized that the validation of water systems is outside the scope of this document.

1.2 Water used in the manufacture of non-sterile medicinal products should comply with the BP, EP or USP monograph for Purified Water. Purified water could be prepared by distillation, by ion exchange, by reverse osmosis (RO) or by any other suitable method from potable water complying with World Health Organization (WHO) standard.

2. REQUIREMENTS FOR WATER SYSTEM

A water system for producing purified water typically consists of carbon filters to remove organic compounds dissolved in feed water, de-ionizers or RO units to remove dissolved solids, filters to remove undissolved solids and bacterial contaminants. Additional features to control microbial growth in water systems include the use of UV irradiation.

2.1 Design of Water System

Many of the design considerations presented below relates to achieving water with good microbiological properties:

2.1.1 Circulating Loop

Water system should be re-circulating to keep water moving (ideally at 1.5m/sec or higher). No flow or low flow conditions are conducive to microbial proliferation and the development of biofilm especially in water distribution pipings. A one-way water system is basically a “dead-leg”.

2.1.2 Piping

2.1.2.1 Piping should be sloped for proper drainage. Normally, BOP (bottom of pipe) elevations must be measured and documented in order to verify the slope to drain (this ensures that the piping can be completely drained).

2.1.2.2 Dead legs should be minimized and eliminated downstream of storage tank. A dead leg is any length of piping more than six diameters away from circulating water.
2.1.2.3 The construction material of choice is stainless steel (e.g. 316L) because of its chemical inertness, ease of sanitization and use over a wide range of temperature. The use of PVC (polyvinyl chloride) should be avoided especially downstream of de-ionizer or RO membrane, because it is prone to biofilm formation. Pipes should have lagging if heated water is circulated to prevent loss of heat.

2.1.2.4 Quality of Weld – typically, in stainless steel piping, orbital welding is used and limit on concavity should be defined (convexities and concavities present at welding are focal points for bacterial growth). In plastic piping, solvent welding is commonly used. Screw fitting or push fit should be avoided.

2.1.3 Valves

Diaphragm valves should preferably be used in water systems, particularly downstream of de-ionizers or RO units, as they could be sanitized effectively. The same restrictions on choice of piping material apply to valves as well.

2.1.4 Storage Tanks

2.1.4.1 Storage tanks should be made of stainless steel. The size of the tank will depend on the demand on the system. Insulation is necessary on storage tanks in high-temperature systems; the tanks may also need to be jacketed in order to heat (or cool) the contents.

2.1.4.2 Storage tanks must be vented to allow for fluctuations in water levels in order to prevent collapse. The vent must be fitted with a sterilizing filter to prevent the air entering the tank from microbiologically contaminating the stored water (the filter should have porosity of less than 1 micron and hydrophobic). Integrity testing of the vent filter shall be performed regularly (e.g. once every 6 or 12 months).
2.1.5 Filters

Filters are commonly found downstream of carbon and resin beds and on the incoming water supply line. They are typically in the mean porosity ranges of 5-50 micron upstream to the resin or RO unit and 1 to 5 microns after the resin or RO units.

2.1.6 Water Point and Use of Flexible Transfer Hoses

Water points should be available at the production areas where water will be used for production. The transfer of treated water to the point of use is done using transfer piping which are made of suitable non-toxic material. These transfer piping should be drained after use and sanitized before use if necessary so that they do not contaminate the water during the transfer process.

2.2 Other Requirements for Water System

2.2.1 Sanitization

There should be written procedures for sanitization of the water system. The water system may be heated to about 80°C for an appropriate holding time and frequency to sanitize the storage tank, distribution piping and valves. Chemical sanitization involving sodium hypochlorite, peracetic acid, hydrogen peroxide or ozone, may be used where appropriate. The frequency of sanitization will depend on validation results.

2.2.2 Maintenance program for carbon beds, resin/RO units and filters etc. The following maintenance procedures, where applicable, should be available:

- Resin regeneration or change procedure
- RO membrane sanitization procedure
- Filter sanitization and change procedure (including filter specifications)
- Carbon bed sanitization and change procedure
- Procedure for sanitization and storage of hoses and other equipment/devices not permanently attached to the water system

Procedure(s) for the shut-down and the start-up of the water system should be available.
2.2.3 Monitoring of water quality

2.2.3.1 Treated water should comply with the chemical and microbiological quality specified in the monograph for Purified Water of official pharmacopoeias such as BP, EP or USP upon installation and before the water is used for routine production.

2.2.3.2 Routine monitoring of water quality should include samples taken at the point(s) of use. The frequency of monitoring should include daily on-line monitoring of conductivity, weekly monitoring for compliance with microbiological specification (total viable count < 100cfu/mL), and monthly monitoring for compliance with full specification/monograph testing, unless otherwise justified by validation results. The above-mentioned chemical and microbiological specifications and those stipulated in the pharmacopoeial monographs for Purified Water are minimum requirements. It should be emphasized that the specifications are not intended to be totally inclusive for every situation where Purified Water as an ingredient is employed. It is therefore incumbent upon the manufacturer to supplement these general guidance notes to fit its particular situation. For example a manufacturer of creams and ointments may wish to test for the absence of *Pseudomonas aeruginosa* on a routine basis if the water used as an ingredient is prepared by ion exchange.

2.2.3.3 Written procedure(s) for monitoring water quality should be available. Alert and action limits should be set and corrective actions to be taken in the event that the limits are exceeded should be documented.

2.2.4 Daily monitoring of key control parameters

Key control parameters, e.g. conductivity, temperature, flow rate and pH of treated water should be monitored on a daily basis and recorded.
2.2.5 Validation of Water System

Validation of the water system should be completed.

3. REFERENCES

3.1 US FDA Guide to Inspections of High Purity Water System
3.2 Proceedings of PIC/S Seminar on “Water for Pharmaceutical Purposes”
3.3 USP 24

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