

## **1 Purpose**

To describe the quality standards required for the production, distribution, use and testing of water used in the manufacture of manufactured materials.

## **2 Scope and Applicability**

This guideline is applicable to all manufacturing functions, departments or manufacturing sites involved in the manufacture, packaging, holding, distribution or testing of active pharmaceutical ingredients, medicinal products, diagnostic agents or medical devices.

## **3 Definitions**

### **3.1 Compendial Water**

Water covered by a compendial monograph. It contains no added substances.

### **3.2 Purified Water**

Water produced by a suitable method (e.g., deionization, reverse osmosis, distillation, etc.) from Potable Water to meet specifications as defined by a compendial monograph.

### **3.3 Highly Purified Water (HPW)**

Water produced from Potable Water by methods including, for example, double-pass reverse osmosis coupled with other suitable techniques such as ultra filtration or deionization. HPW (Highly Purified Water) meets the same quality standards as WFI (Water for Injections) but the production methods are considered less reliable than distillation and thus it is considered unacceptable for use as WFI.

### **3.4 Water For Injections (WFI)**

Water produced by a suitable method (e.g. distillation) from Potable Water, usually with an intermediate purification step(s), to meet specifications as defined by a compendial monograph.

### **3.5 Suitable Non-Compendial Water**

Water not covered by a compendial monograph. As a minimum it complies with appropriate drinking water regulations.

The water may also have additional treatment, with appropriate higher quality attributes, to meet particular process requirements.

### **3.6 Potable Water**

Water, that as a minimum, meets national standards for water intended for human consumption that have been documented as at least equivalent to World Health Organization (WHO) guidelines.

The national standards for the USA, Europe and Japan meet or exceed the WHO

- Location of sampling points
- Quantity of sample required
- Sampling instructions
- Sample storage including any time limitations to perform the analysis
- Training of samplers

Samples should be collected from points of use in the same way as, or in a manner that simulates how the water is used during routine production. Where possible samples will be taken on a rotational basis to ensure that points are not always sampled on the same day.

Samples that are not taken from points of use, and which may be taken from a sample point that is exposed to the elements, may be flushed for a defined time to ensure the sample reflects the water in the system. See Appendix 1 for suggested minimum sampling frequencies.

## **5.2 Testing**

Written, approved and validated test methods are required. Test methods as per the EP or United States Pharmacopeia (USP) are considered validated.

### **5.2.1 Potable Water**

Testing for the full analytical requirements for Potable Water is usually outside the scope of the typical pharmaceutical laboratory. The recommended practice is to receive Analytical Reports and/or Certificates of Analysis from the municipality/supply company providing the water, together with supporting local test data.

If alternative sources of water are used, e.g. borehole/well water, it may be possible to arrange for the local municipality/supply company or a contract water-testing laboratory to sample and test the water against the appropriate standard.

The local site should perform a limited number of analytical monitoring tests that have been pre-established in a local procedure or standard.

### **5.2.2 Purified Water**

The tests, methodology and specifications for Purified Water are described in the relevant Pharmacopoeias.

### **5.2.3 Endotoxin-Controlled Purified Water**

The tests, methodology and specifications for Endotoxin-Controlled Purified Water are, as minimum, the same as for Purified Water with the addition of the Bacterial Endotoxin Test with a limit of not more than 0.25 IU/ml.

### **5.2.4 HPW**

The tests, methodology and specifications for HPW are described in the EP.

The exact nature of the testing is determined by the specification claimed for the water system, i.e. Purified Water USP, EP, etc.

#### **5.4.3 Endotoxin-Controlled Purified Water**

Analytical testing frequency would be as for Purified Water.

#### **5.4.4 HPW**

Analytical testing of a HPW system would typically be performed weekly. As with Purified Water and WFI systems it is now common to install in-line meters to perform TOC and Conductivity measurements.

#### **5.4.5 WFI**

Analytical testing of a WFI system would typically be performed weekly. As with Purified Water systems it is now common to install in-line meters to perform TOC and Conductivity measurements.

#### **5.4.6 Pure Steam**

Analytical testing of Pure Steam condensate would typically be performed monthly.

### **5.5 Storage and Distribution**

Particular care is required for the storage and distribution of water. The major concern is maintaining the microbiological quality of the water. Typically enough Potable Water is held in a buffer or break tank to provide a uniform flow and working pressure for the user point(s) and/or treatment system. Should it be necessary to hold larger quantities of Potable Water then an anti-microbial pre-treatment step is likely to be required. Depending on the quantity being held various options include the use of UV light, ozone addition or chlorination, although any chemical added must not exceed the Potable Water quality standards.

Any chemicals added during pre-treatment or subsequent conversion to Purified Water or other higher quality waters must be removed as part of the purification process

Purified Water and Endotoxin-Controlled Purified Water is usually held and distributed in stainless steel vessels and pipes although plastic alternatives have been successfully used. It is typical to make use of hygienic designs, provide re-circulating distribution systems and to provide for routine sanitization to maintain the quality of stored Purified Water. It is possible to add ozone to the storage tank and to remove the ozone with UV light during distribution. Periodically turning off the UV light and letting the ozonated water circulate for an appropriate time will sanitise the distribution system. An alternative method with stainless steel systems is to periodically heat the Purified Water to about 80 °C and circulate the heated water through the distribution system for an appropriate time before

## 5.7 Validation

In common with other pharmaceutical systems, water and steam pre-treatment, generation and distribution systems that impact on product quality require validation to establish critical process parameters and their operating ranges. A unique facet of validation of a water system is that it can take at least one year to complete all of the testing so as to encompass all of the seasonal effects on the water supply. After successful installation and operational qualification activities, an extensive period of performance testing is undertaken to complete the validation. Typically, an initial period of one month of extensive sampling (up to each point each day) and testing throughout the pre-treatment, generation and distribution system to establish operating conditions is followed by a further month of extensive sampling/testing to demonstrate the system is under control. If the results are satisfactory the system can be released for use with the number of tests performed over the one-year period decreased to that required for routine operation. Critical process parameters should be regularly monitored to ensure compliance with the validated ranges.

Any changes to an existing system must be controlled through appropriate procedures and the requirements for assuring quality assessed accordingly.

Additional sampling will be required, taken from those points affected and for a time appropriate to the change. As a guide, at least two weeks of intensive data, operating with normal procedures would be expected, with samples taken from the affected points twice per week for chemical analysis and daily for microbiological/endotoxin analysis as appropriate.

## 5.8 Trending and Review

Microbiological and analytical quality data from water pre-treatment, production and distribution systems should be regularly trended and reviewed to identify problems and focus attention where corrective action is required to maintain the required water quality.

Regular reviews of supporting information, e.g. operating performance, changes, should be performed in conjunction with the water quality data to provide assurance that the system continues to be operated in a validated state.

## 5.9 System Maintenance

All water systems should be subject to defined maintenance programs and schedules together with the appropriate specification/calibration of critical instruments.

## 5.10 Change Control

All modifications to the, e.g. installation, operation, control and sampling, of water systems should be subject to appropriate change control procedures.

## Manual 042 Water Quality Standard

Class 3: exception basis only, e.g. investigating results Out of Specification (OOS) and/or exceeding the Action Limit.

### **HPW & WFI**

Class 1: at least one point each day with each point of use tested at least weekly.

Class 2: monthly

Class 3: exception basis only, e.g. investigating results Out of Specification (OOS) and/or exceeding the Action Limit.

### **PURE STEAM (CONDENSATE)**

Class 1: at least one point, plus the supply from the Pure Steam Generator (PSG) is tested monthly.

Class 2: quarterly.

Class3: exception basis only, e.g. investigating results Out of Specification (OOS) and/or exceeding the Action Limit.

Manual 042 Water Quality Standard

|  |  |   |  |   |
|--|--|---|--|---|
| formulation  |  |   |  |   |
| Sterile API for sterile non-parenteral formulation |  | X |  |   |
| Sterile and apyrogenic API and formulation         |  |   |  | X |

Note:

(\*)

Purified Water should be used where there are technical requirements for greater chemical purity

**For Sterile or Sterile, Apyrogenic Product where Water is Present in the Formulation:**

| <b>Sterile or Sterile Apyrogenic Formulations</b> | <b>Potable Water</b> | <b>Purified Water</b> | <b>Endotoxin Controlled Purified Water</b> | <b>Water for Injections</b> |
|---|----------------------|-----------------------|--|-----------------------------|
| Parenteral  |                      |                       |  | X                           |
| Ophthalmic  |                      | X                     |  |                             |
| Haemofiltration                                   |                      |                       |  | X                           |
| Haemodiafiltration                                |                      |                       |  | X                           |
| Peritoneal Dialysis                               |                      |                       |  | X                           |
| Irrigation  |                      |                       |  | X                           |
| Nasal/Ear   |                      | X                     |  |                             |
| Cutaneous   |                      | X                     |  |                             |
| Nebuliser*  |                      |                       |  | X                           |

**For Non-Sterile Product where Water is Present in the Final Formulation:**

| <b>Non-Sterile Product</b> | <b>Potable Water</b> | <b>Purified Water</b> | <b>Endotoxin Controlled Purified Water</b> | <b>Water for Injections</b> |
|----------------------------|----------------------|-----------------------|--|-----------------------------|
| Oral                       |                      | X                     |  |                             |
| Nebuliser*                 |                      | X                     |  |                             |
| Cutaneous                  |                      | X**                   |  |                             |
| Nasal/Ear                  |                      | X                     |  |                             |
| Rectal/Vaginal             |                      | X                     |  |                             |

Note:

(\*) In certain disease states, medicinal products administered by nebulisation are required to be sterile and non-pyrogenic. In such cases, WFI or sterilised HPW should be used.

(\*\*) For some products it may be acceptable to use Potable Water where justified and authorized taking into account the variability in quality.