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

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 sanities the distribution system. An alternative method with stainless steel systems is to periodically heat the Purified Water to about 80 ºC and circulate the heated water through the distribution system for an appropriate time before cooling back to ambient temperature.

Steam sanitisation of systems with Pure Steam may be possible although this

Appendix 2

REQUIREMENTS FOR WATER QUALITY FOR DIFFERENT USES

The minimum qualities of water that must be used at different manufacturing stages are tabulated below.

For Manufacturing the Intermediate of an API:

Intermediate (IM) of Active Pharmaceutical Ingredient (API)	Potable Water	Purified Water	Endotoxin Controlled Purified Water	Water for Injections
No requirement for sterility or apyrogenicity	X*			
Non-sterile IM and API for sterile, non-parenteral	X*			
Non-sterile IM and API for use in sterile parenteral		X		
Non-sterile IM for sterile API for sterile non- parenteral		X		
Non-sterile IM for sterile API for sterile parenteral			X	
Sterile IM and API for sterile non-parenteral		X		
Sterile, apyrogenic IM, API and formulation				X

Note:
(*)
Purified Water should be used where there are technical requirements for greater chemical purity.

For early stages of intermediate manufacture it may be acceptable to use Potable Water, or better, where justified and authorized taking into account the variability in quality of Potable Water.

