

# GUIDANCE DOCUMENT

## REFERENCE VERSION



<b>HIGH PURITY WATER SYSTEMS</b>
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## 1. PURPOSE

To provide guidance on the development of High Purity Water System Validation packages to meet the Current Good Manufacturing Practice (CGMP) requirements of both the [American \(FDA references shown in blue\)](#) and [European \(EC references shown in red\)](#) regulatory bodies.

## 2. SCOPE

This guide is intended for the validation of compendial grade water systems used in the manufacture of Finished Pharmaceuticals (Medicinal Products) and Active Pharmaceutical Ingredients (APIs).

## 3. INTRODUCTION

This guide contains **over 250** American and European CGMP regulatory points for consideration when developing validation packages for compendial grade water systems used in the manufacture of Finished Pharmaceuticals (Medicinal Products) and Active Pharmaceutical Ingredients (APIs).

The term "points for consideration" should be emphasised. The guide is intended to present the American and European regulatory statements on this topic side by side in a single reference text. The applicability of these statements will depend on the unique system under consideration.

The points have been extracted following a detailed review of:

- over **250 regulatory texts**
- over **8,000 regulatory records**
- over **1,500 warning letter extracts**
- over **2,000 FDA 483 observations**
- **to date issues** of the FDA's **Human Drug CGMP Notes**
- the **ISPE Baseline Guide - Water and Steam Systems (First Edition, January 2001)**

Each point for consideration within the guide is supported by one or more regulatory references from which it was derived. [American references are shown in blue](#) and [European references are shown in red](#). Selected [American](#) references, available under the Freedom of Information Act, are included in full.

For ease of review the points have been collated under logical sub-headings. The author appreciates that the grouping of the points is subjective.

## 4. SUMMARY

Water is the most widely used substance, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbiological quality of these waters is important because proliferation of microorganisms ubiquitous to water may occur during the purification, storage, and distribution of this substance. If water is used in the final product, these microorganisms or their metabolic products may eventually cause adverse consequences.

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**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03**

(Para 1)  
[ViP ID: 2554]

"Water is the most widely used substance, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbiological quality of these waters is important because proliferation of microorganisms ubiquitous to water may occur during the purification, storage, and distribution of this substance. If water is used in the final product, these microorganisms or their metabolic products may eventually cause adverse consequences."

## 5. DESIGN GUIDANCE

Detailed guidance on the design of compendial grade water systems is presented in the ISPE Baseline Guide for Water and Steam Systems (First edition, January 2001). The scope of the Baseline Guide is restricted to the design, construction and operation of new water and steam systems, and is intended primarily for regulatory compliance for the domestic United States (US) market. The baseline guide has been organised to assist in a logical decision process to determine the type of water required and the system design needed to provide it.

This section is a compilation of regulatory extracts presented to supplement the early chapters of the Baseline guide to assist in this decision making process.

### 5.1 Water Quality

#### 5.1.1 Drinking Water

1. Drinking water is not covered by a compendial monograph but must comply with the quality attributes of the EPA NPDWR or comparable regulations of the European Union or Japan. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources. Drinking Water may be used in the early stages of chemical synthesis and in the early stages of the cleaning of pharmaceutical manufacturing equipment. It is the prescribed source feed water for the production of pharmaceutical waters. As seasonal variations in the quality attributes of the drinking water supply can occur, processing steps in the production of pharmaceutical waters must be designed for this characteristic.

**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03**  
**TYPES OF WATER**  
**DRINKING WATER**  
[ViP ID: 2556]

"Drinking water is not covered by a compendial monograph but must comply with the quality attributes of the EPA NPDWR or comparable regulations of the European Union or Japan. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources. Drinking Water may be used in the early stages of chemical synthesis and in the early stages of the cleaning of pharmaceutical manufacturing equipment. It is the prescribed source feed water for the production of pharmaceutical waters. As seasonal variations in the quality attributes of the drinking water supply can occur, processing steps in the production of pharmaceutical waters must be designed for this characteristic."

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### 5.1.2 System Feed Water

1. For the manufacture of drug substances that are not for parenteral use, there is still a microbiological concern, although not to the same degree as for parenteral grade drug substances. In some areas of the world, Potable (chlorinated) water may not present a microbiological problem. However, there may be other issues. For example, chlorinated water will generally increase chloride levels. In some areas, process water may be obtained directly from neutral sources.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**XIII PROCESS WATER**

(para 4)

[ViP ID: 1009]

"For the manufacture of drug substances that are not for parenteral use, there is still a microbiological concern, although not to the degree as for parenteral grade drug substances. In some areas of the world, Potable (chlorinated) water may not present a microbiological problem. However, there may be other issues. For example, chlorinated water will generally increase chloride levels. In some areas, process water may be obtained directly from neutral sources."

2. The bacterial quality of the feedwater used to produce pure steam and WFI should be monitored.

Interpreted from GMP Trends, Issue #515, 01 July 1998

Manufacturing - Sterile Product Controls

Item 2

[ViP ID: 6422]

### 5.1.3 Formulation Water

1. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in Figure 3 of USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03, PHARMACEUTICAL WATER SYSTEMS.

**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03**

**PHARMACEUTICAL WATER SYSTEMS**

[ViP ID: 2567]

"The quality attributes of water for a particular application are dictated by the requirements of its usage. Sequential processing steps that are used for treating water for different pharmaceutical purposes are shown in Figure 2. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in Figure 3. These diagrams may be used to assist in defining requirements for specific water uses and in the selection of unit operations."

2. Different products require different quality waters. Parenterals require very pure water with no endotoxins. Topical and oral products require less pure water and do not have a requirement for endotoxins. Even with topical and oral products there are factors that dictate different qualities for water. For example, preservatives in antacids are marginally effective, so more stringent microbial limits have to be set. The quality control department should assess each product manufactured with the water from their system and determine the microbial action limits based on the most microbial sensitive product. In lieu of stringent water action limits in the system the manufacturer can add a microbial reduction step in the manufacturing process for the sensitive drug product(s).

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**I SYSTEM DESIGN**

(para 5)

[ViP ID: 951]

"Finally, and possibly the most important consideration, is the risk assessment or level of quality that is desired. It should be recognized that different products require different quality waters. Parenterals require very pure water with no endotoxins. Topical and oral products require less pure water and do not have a requirement for endotoxins. Even with topical and oral products there are factors [factors] that dictate different qualities for water. For example, preservatives in antacids are marginally effective, so more stringent microbial limits have to be set. The quality control department should assess each product manufactured with the water from their system and determine the microbial action limits based on the most microbial sensitive product. In lieu of stringent water action limits in the system the manufacturer can add a microbial reduction step in the manufacturing process for the sensitive drug product(s)."

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- Currently, the USP, pg. 4, in the General Notices Section, allows drug substances to be manufactured from Potable Water. It comments that any dosage form must be manufactured from Purified Water, Water For Injection, or one of the forms of Sterile Water. There is some inconsistency in these two statements, since Purified Water has to be used for the granulation of tablets, yet Potable Water can be used for the final purification of the drug substance.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**XIII PROCESS WATER**

(para 1)

[ViP ID: 1006]

"Currently, the USP, pg. 4, in the General Notices Section, allows drug substances to be manufactured from Potable Water. It comments that any dosage form must be manufactured from Purified Water, Water For Injection, or one of the forms of Sterile Water. There is some inconsistency in these two statements, since Purified Water has to be used for the granulation of tablets, yet Potable Water can be used for the final purification of the drug substance."

#### 5.1.4 Purified Water

- Purified Water (see USP monograph) is used as an excipient in the production of official preparations; in pharmaceutical applications, such as cleaning of certain equipment; and in the preparation of some bulk pharmaceutical chemicals. Purified Water must meet the requirements for ionic and organic chemical purity and must be protected from microbial proliferation. It is prepared using Drinking Water as a feed water and is purified using unit operations that include deionization, distillation, ion-exchange, reverse osmosis, filtration, or other suitable procedures. Purified Water systems must be validated.

Purified Water systems that produce, store, and circulate water under ambient conditions are susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.

**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03**

**TYPES OF WATER**

**PURIFIED WATER**

[ViP ID: 2557]

"... Purified Water (see USP monograph) is used as an excipient in the production of official preparations; in pharmaceutical applications, such as cleaning of certain equipment; and in the preparation of some bulk pharmaceutical chemicals. Purified Water must meet the requirements for ionic and organic chemical purity and must be protected from microbial proliferation. It is prepared using Drinking Water as a feed water and is purified using unit operations that include deionization, distillation, ion-exchange, reverse osmosis, filtration, or other suitable procedures. Purified Water systems must be validated.

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#### 5.1.5 Water For Injection

- Water for Injection (see USP monograph) is an excipient in the production of injections and for use in pharmaceutical applications, such as cleaning of certain equipment, and in the preparation of some bulk pharmaceutical chemicals. The source or feed water for this article is Drinking Water, which may have been preliminarily purified but which is finally subjected to distillation or reverse osmosis. It must meet all of the chemical requirements for Purified Water and in addition the requirements under Bacterial Endotoxins Test <85>. It also must be protected from microbial contamination. The system used to produce, store, and distribute Water for Injection must be designed to prevent microbial contamination and the formation of microbial endotoxins, and it must be validated.

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**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03**  
**TYPES OF WATER**  
**WATER FOR INJECTION**  
[ViP ID: 2559]

"...Water for Injection (see USP monograph) is an excipient in the production of injections and for use in pharmaceutical applications, such as cleaning of certain equipment, and in the preparation of some bulk pharmaceutical chemicals. The source or feed water for this article is Drinking Water, which may have been preliminarily purified but which is finally subjected to distillation or reverse osmosis. It must meet all of the chemical requirements for Purified Water and in addition the requirements under Bacterial Endotoxins Test <85>. It also must be protected from microbial contamination. The system used to produce, store, and distribute Water for Injection must be designed to prevent microbial contamination and the formation of microbial endotoxins, and it must be validated."

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**  
( July, 1993)  
**III MICROBIAL LIMITS**  
Water For Injection Systems  
(para 3)  
[ViP ID: 964]

"The real concern in WFI is endotoxins. Because WFI can pass the LAL endotoxin test and still fail the above microbial action limit, it is important to monitor WFI systems for both endotoxins and microorganisms."

## 5.2 Microbial Limits

1. The individual monographs for Purified Water and Water for Injection do not include specific microbial limits. These were purposefully omitted since most current microbiological techniques available require at least 48 hours to obtain definitive results. By that time, the water from which the sample was taken has already been employed in the production process. Failure to meet a compendial specification would require rejecting the product lot involved, and this is not the intent of an alert or action guideline. The establishment of quantitative microbiological guidelines for water for pharmaceutical purposes is in order because such guidelines will establish procedures that are to be implemented in the event that significant excursions beyond these limits occur.

**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 – 03**  
**ALERT AND ACTION LEVELS**  
(para 1)  
[ViP ID: 2616]

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2. For purified water systems, microbiological specifications are not as clear. USP XXII specifications, that it complies with federal Environmental Protection Agency regulations for drinking water, are recognized as being minimal specifications. There have been attempts by some to establish meaningful microbiological specifications for purified water. The CFTA proposed a specification of not more than 500 organisms per ml. The USP XXII has an action guideline of not greater than 100 organisms per ml. Although microbiological specifications have been discussed, none (other than EPA standards) have been established. Agency policy is that any action limit over 100 CFU/mL for a purified water system is unacceptable.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**  
( July, 1993)  
**III MICROBIAL LIMITS**  
Purified Water Systems  
(para 1)  
[ViP ID: 965]

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"For purified water systems, microbiological specifications are not as clear. USP XXII specifications, that it complies with federal Environmental Protection Agency regulations for drinking water, are recognized as being minimal specifications. There have been attempts by some to establish meaningful microbiological specifications for purified water. The CFTA proposed a specification of not more than 500 organisms per ml. The USP XXII has an action guideline of not greater than 100 organisms per ml. Although microbiological specifications have been discussed, none (other than EPA standards) have been established. Agency policy is that any action limit over 100 CFU/mL for a purified water system is unacceptable."

ISPE Baseline Guide - Water and Steam Systems  
(First Edition, January 2001)  
2. KEY DESIGN PHILOSOPHIES  
2.3.1 Specifying Water Quality

3. In the CGMP context firms should set and justify their own microbial limits for purified water (PW) based on at least two factors in production. First is the microbial specification of the finished product or the equipment surfaces which contact the water. The microbial limit for the water as a component should be more stringent than the limit set for the end product. For example, where a finished product has a microbial limit of not more than 100 cfu/ml, the corresponding limit for water as an ingredient in that product should be less than 100 cfu/ml.

The second factor is the validated water system's operational data. Properly controlled and well designed PW systems should be capable of producing validated water quality in the range of 30-50 cfu/ml. Such operational data would not justify establishing a less stringent specification of "not more than 100 cfu/ml."

HUMAN DRUG CGMP NOTES, VOLUME 5, NUMBER 1  
(March, 1997)

Motise's Notebook

Policy Questions:

Question 4

Contact for further information: Michael J. Verdi, HFD-322, 301-594-0095; e-mail: verdim@cder.fda.gov

Reference: 21 CFR 211.113, Control of microbiological contamination; 211.84(c)(6), Testing and approval or rejection of components, drug product containers, and closures.

"What should firms use as microbial limits for purified water?"

In the CGMP context firms should set and justify their own microbial limits for purified water (PW) based on at least two factors in production. First is the microbial specification of the finished product or the equipment surfaces which contact the water. The microbial limit for the water as a component should be more stringent than the limit set for the end product. For example, where a finished product has a microbial limit of not more than 100 cfu/ml, the corresponding limit for water as an ingredient in that product should be less than 100 cfu/ml.

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ISPE Baseline Guide - Water and Steam Systems  
(First Edition, January 2001)  
2. KEY DESIGN PHILOSOPHIES  
2.2.3 Non-Monographed but accepted requirements

ISPE Baseline Guide - Water and Steam Systems  
(First Edition, January 2001)  
2. KEY DESIGN PHILOSOPHIES  
2.3.1 Specifying Water Quality

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- The USP gives some guidance in their monograph on Microbiological Attributes of Non-Sterile Products. It points out that, "The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential harm to the user." Thus, not just the indicator organisms listed in some of the specific monographs present problems. It is up to each manufacturer to evaluate their product, the way it is manufactured, and establish an acceptable action level of contamination, not to exceed the maximum, for the water system, based on the highest risk product manufactured with the water.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**III MICROBIAL LIMITS**

Purified Water Systems

(para 5)

[ViP ID: 969]

"The USP gives some guidance in their monograph on Microbiological Attributes of Non-Sterile Products. It points out that, "The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential harm to the user." Thus, not just the indicator organisms listed in some of the specific monographs present problems. It is up to each manufacturer to evaluate their product, the way it is manufactured, and establish an acceptable action level of contamination, not to exceed the maximum, for the water system, based on the highest risk product manufactured with the water."

- The purpose of establishing any action limit or level is to assure that the water system is under control. Any action limit established will depend upon the overall purified water system and further processing of the finished product and its use. For example, purified water used to manufacture drug products by cold processing should be free of objectionable organisms.

"Objectionable Organisms" are any organisms that can cause infections when the drug product is used as directed or any organism capable of growth in the drug product. As pointed out in the Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, the specific contaminant, rather than the number is generally more significant.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**III MICROBIAL LIMITS**

Purified Water Systems (para 2)

[ViP ID: 966]

The purpose of establishing any action limit or level is to assure that the water system is under control. Any action limit established will depend upon the overall purified water system and further processing of the finished product and its use. For example, purified water used to manufacture drug products by cold processing should be free of objectionable organisms.

We have defined "objectionable organisms" as any organisms that can cause infections when the drug product is used as directed or any organism capable of growth in the drug product. As pointed out in the Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, the specific contaminant, rather than the number is generally more significant.

- Monitoring data should be analyzed on an ongoing basis to ensure that the process continues to perform within acceptable limits. An analysis of data trends is often used to evaluate process performance. This information can be used to predict departures from established operating parameters, thereby signaling the need for appropriate preventative maintenance. It should be recognized that the microbial Alert and Action Levels established for any pharmaceutical water system are necessarily linked to the monitoring method chosen. Using the recommended methodologies, generally considered appropriate Action Levels are 500 colony-forming units (cfu) per mL for Drinking Water, 100 cfu per mL for Purified Water and 10 cfu per 100 mL for Water for Injection. It should be emphasized that the above action guidelines are not intended to be totally inclusive for every situation where ingredient waters are employed. For example, Gram negative microorganisms are not excluded from ingredient waters, nor is the presence of Gram negative microorganisms prohibited in Drinking Water in the Federal Regulations. The reason for this is that these microorganisms are ubiquitous to the aqueous environment and their exclusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing scenarios. However, there are situations where they might not be tolerated: in topical products and in some oral dosage forms. It is, therefore, incumbent upon the manufacturer to supplement the general action guidelines to fit each particular manufacturing situation.

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**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03  
ALERT AND ACTION LEVELS  
(para 6)  
[ViP ID: 2621]**

"Monitoring data should be analyzed on an ongoing basis to ensure that the process continues to perform within acceptable limits. An analysis of data trends is often used to evaluate process performance. This information can be used to predict departures from established operating parameters, thereby signaling the need for appropriate preventative maintenance. It should be recognized that the microbial Alert and Action Levels established for any pharmaceutical water system are necessarily linked to the monitoring method chosen. Using the recommended methodologies, generally considered appropriate Action Levels are 500 colony-forming units (cfu) per mL for Drinking Water, 100 cfu per mL for Purified Water and 10 cfu per 100 mL for Water for Injection. It should be emphasized that the above action guidelines are not intended to be totally inclusive for every situation where ingredient waters are employed. For example, Gram negative microorganisms are not excluded from ingredient waters, nor is the presence of Gram negative microorganisms prohibited in Drinking Water in the Federal Regulations. The reason for this is that these microorganisms are ubiquitous to the aqueous environment and their exclusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing scenarios. However, there are situations where they might not be tolerated: in topical products and in some oral dosage forms. It is, therefore, incumbent upon the manufacturer to supplement the general action guidelines to fit each particular manufacturing situation."

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS  
(July, 1993)  
III MICROBIAL LIMITS  
Water For Injection Systems  
(para 1)  
[ViP ID: 962]**

"Regarding microbiological results, for Water For Injection, it is expected that they be essentially sterile. Since sampling frequently is performed in non-sterile areas and is not truly aseptic, occasional low level counts due to sampling errors may occur. Agency policy, is that less than 10 CFU/100ml is an acceptable action limit. None of the limits for water are pass/fail limits. All limits are action limits."

**ISPE Baseline Guide - Water and Steam Systems  
(First Edition, January 2001)  
2. KEY DESIGN PHILOSOPHIES  
2.2.3 Non-Monographed but accepted requirements**

**ISPE Baseline Guide - Water and Steam Systems  
(First Edition, January 2001)  
2. KEY DESIGN PHILOSOPHIES  
2.3.1 Specifying Water Quality**

- Thus, in establishing the level of contamination allowed in a high purity water system used in the manufacture of a non-sterile product requires an understanding of the use of the product, the formulation (preservative system) and manufacturing process. For example, antacids, which do not have an effective preservative system, require an action limit below the 100 CFU/mL maximum.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS  
(July, 1993)  
III MICROBIAL LIMITS  
Purified Water Systems  
(para 4)  
[ViP ID: 968]**

"Thus, in establishing the level of contamination allowed in a high purity water system used in the manufacture of a non-sterile product requires an understanding of the use of the product, the formulation (preservative system) and manufacturing process. For example, antacids, which do not have an effective preservative system, require an action limit below the 100 CFU/mL maximum."

- Microbial specifications for water should be based on historical trend data.

**Interpreted from GMP Trends, Issue #559, 01 May 2000  
Manufacturing - Sterile Product Controls  
Item 3  
[ViP ID: 15050]**

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9. Manufacturing processes for API's which are pyrogen tested and intended for use in the manufacture of intravenous solutions and injectable finished products include endotoxin specifications for the DI water used during final isolation and purification.

**Interpreted from GMP Trends, Issue #559, 01 May 2000**  
**Manufacturing - Active Pharmaceutical Ingredients (API)**  
**Item 5**  
**[ViP ID: 15020]**

10. The production and/or storage of non-sterile water that may be of reagent grade or used as a buffer is evaluated from both a stability and microbiological aspect.

**REG 11/01/91 BIOTECHNOLOGY INSPECTION GUIDE (November, 1991)**  
**EXTRACTION, ISOLATION AND PURIFICATION**  
**E. Process Water/Buffers/WFI**  
**(para 4)**  
**[ViP ID: 1078]**

**"The production and/or storage of non-sterile water that may be of reagent grade or used as a buffer should be evaluated from both a stability and microbiological aspect."**

11. Deionised water system alert limits should be based on historical data.

**Interpreted from GMP Trends, Issue #623, 01 Jan 2003**  
**Manufacturing Controls**  
**Item 2b**  
**[ViP ID: 51360]**

12. Alert and action level failures should be investigated to determine corrective and preventative actions.

**Extracted from FDA warning letter**  
**UK**  
**07-Nov-02**  
**[ViP ID: 57260]**

"2(b). Failure to establish and maintain procedures for implementing corrective and preventive action and investigating the cause of nonconformities in processes and the quality system, as required by 21 CFR 820-100(a)(2). For example:

(b)The following months water samples taken on 12/11/01 revealed that the sample taken from the [redacted] exceeded alert levels. There was no investigation into why this occurred. The only action by your firm was to [redacted] on 1/2/02 and because the results were [redacted] the [redacted]."

13. Microbial testing of purified water should be performed to demonstrate it is suitable for its intended use.

**Extracted from FDA warning letter W/L 08-03**  
**USA**  
**19-Nov-02**  
**[ViP ID: 54340]**

"1. Failure to establish and follow adequate procedures to show that each lot of a component (purified water) that is liable to microbiological contamination that is objectionable in view of its intended use, is subjected to adequate microbiological tests before use [21 CFR 211.84(d)(6)]. Specifically, our investigators observed that the purified water system that is used for manufacturing sterile ophthalmic drugs is not adequately controlled or monitored. Your firm failed to investigate high microbiological counts on samples collected on 1/4/02. In addition, on 1/6/02, samples were collected from two locations not specified in procedures as sample locations, reportedly because the bacterial counts from two point of use outlets were "still high after sanitization"."

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<b>Author</b> : Mark Hodkinson	High Purity Water Systems	<b>Date:</b> : 08 September 2004

### 5.3 Generation System

1. For economic reasons, many of the biotech companies manufacture WFI by reverse osmosis rather than by distillation. Most of these systems have been found to be contaminated. Typically, they employ plastic pipe (PVC) and non-sealed storage tanks, which are difficult to sanitize.

**REG 11/01/91 BIOTECHNOLOGY INSPECTION GUIDE (November, 1991)**  
**EXTRACTION, ISOLATION AND PURIFICATION**  
**E. Process Water/Buffers/WFI**  
 (para 2)  
 [ViP ID: 1076]

"For economic reasons, many of the biotech companies manufacture WFI by reverse osmosis rather than by distillation. Most of these systems have been found to be contaminated. Typically, they employ plastic pipe (PVC) and non-sealed storage tanks, which are difficult to sanitize. Any threads or drops in a cold system provide an area where microorganisms can lodge and multiply. Some of the systems employ a terminal sterilizing filter. However, the primary concern is endotoxins, and the terminal filter may merely serve to mask the true quality of the WFI used. The limitations of relying on a 0.1 ml sample of WFI for endotoxins from a system should also be recognized. The system should be designed to deliver high purity water, with the sample merely serving to assure that it is operating adequately. As with other WFI systems, if cold WFI water is needed, point-of-use heat exchangers can be used."

2. In the bulk drug substance industry, particularly for parenteral grade substances, it is common to see Ultrafiltration (UF) and Reverse Osmosis (RO) systems in use in water systems. While ultrafiltration may not be as efficient at reducing pyrogens, they will reduce the high molecular weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it will reduce numbers. Additionally, as previously discussed with other cold systems, there is considerable maintenance required to maintain the system.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**  
 (July, 1993)  
**XIII PROCESS WATER**  
 (para 3)  
 [ViP ID: 1008]

"In the bulk drug substance industry, particularly for parenteral grade substances, it is common to see Ultrafiltration (UF) and Reverse Osmosis (RO) systems in use in water systems. While ultrafiltration may not be as efficient at reducing pyrogens, they will reduce the high molecular weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it will reduce numbers. Additionally, as previously discussed with other cold systems, there is considerable maintenance required to maintain the system."

3. Many of the comments regarding equipment for WFI systems are applicable to Purified Water Systems. One type system that has been used to control microbiological contamination utilizes ozone. Although the system has purported to be relatively inexpensive, there are some problems associated with it. For optimum effectiveness, it is required that dissolved ozone residual remain in the system. This presents both employee safety problems and use problems when drugs are formulated.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**  
 (July, 1993)  
**XI PURIFIED WATER SYSTEMS**  
 (para 1)  
 [ViP ID: 999]

"Many of the comments regarding equipment for WFI systems are applicable to Purified Water Systems. One type system that has been used to control microbiological contamination utilizes ozone. Figure 10 illustrates a typical system. Although the system has purported to be relatively inexpensive, there are some problems associated with it. For optimum effectiveness, it is required that dissolved ozone residual remain in the system. This presents both employee safety problems and use problems when drugs are formulated."

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## 5.4 Distribution System

- Whether a system is circulating or one-way is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant. A one-way water system is basically a "dead-leg".

### REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

(July, 1993)

#### I SYSTEM DESIGN

(para 4)

[ViP ID: 950]

"Whether a system is circulating or one-way is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant. A one-way water system is basically a 'dead-leg'."

### USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03

#### PURIFIED WATER AND WATER FOR INJECTION SYSTEMS

##### DISTRIBUTION

[ViP ID: 2588]

"...Distribution configuration should allow for the continuous flow of water in the piping by means of recirculation or should provide for the periodic flushing of the system. Experience has shown that continuously recirculated systems are easier to maintain."

### ISPE Baseline Guide - Water and Steam Systems

(First Edition, January 2001)

#### 2. KEY DESIGN PHILOSOPHIES

##### 2.5 CGMP COMPLIANCE ISSUES

- At a reinspection of this facility, it was noted that they corrected the deficient water system with a circulating stainless steel piping system that was fed by four RO units in series. Because this manufacturer did not have a need for a large amount of water (the total system capacity was about 30 gallons), they attempted to let the system sit for approximately one day. At zero time (at 9 AM on 3/10), there were no detectable levels of microorganisms and of endotoxins. After one day, this static non-circulating system was found to be contaminated. The four consecutive one hour samples also illustrate the variability among samples taken from a system. After the last sample at 12 PM was collected, the system was resanitized with 0.5% peroxide solution, flushed, recirculated and resampled. No levels of microbiological contamination were found on daily samples after the system was put back in operation. This is the reason the agency has recommended that non-recirculating water systems be drained daily and water not be allowed to sit in the system.

### REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

(July, 1993)

#### X Reverse Osmosis

(para 9)

[ViP ID: 998]

"At a reinspection of this facility, it was noted that they corrected the deficient water system with a circulating stainless steel piping system that was fed by four RO units in series. Because this manufacturer did not have a need for a large amount of water (the total system capacity was about 30 gallons), they attempted to let the system sit for approximately one day. Figure 9 shows that at zero time (at 9 AM on 3/10), there were no detectable levels of microorganisms and of endotoxins. After one day, this static non-circulating system was found to be contaminated. The four consecutive one hour samples also illustrate the variability among samples taken from a system. After the last sample at 12 PM was collected, the system was resanitized with 0.5% peroxide solution, flushed, recirculated and resampled. No levels of microbiological contamination were found on daily samples after the system was put back in operation. This is the reason the agency has recommended that non-recirculating water systems be drained daily and water not be allowed to sit in the system."

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## 5.5 Pipework Specification

1. The following extract has been taken from the FDA's "Human Drug CGMP Notes", which is a memo issued to FDA personnel periodically to provide guidance on CGMP for human use pharmaceuticals.

***Does FDA "prefer" polyvinylidene difluoride over stainless steel for construction of recirculating loops in water for injection (WFI) systems?***

There is no official agency preference for one material over another. Whatever material a firm selects for its water for injection system must be suitable for the intended use. This holds true for virtually any production equipment.

In the case of a WFI system, factors to consider in evaluating the suitability of the piping would include interior smoothness, the ability to withstand high temperatures and pressures, and the ability to hold up to sterilizing and sanitizing agents.

As a general matter, equipment surfaces that contact components, in-process materials, or drug products must not be reactive, additive, or absorptive so as to alter the drug product's safety, identity, strength, quality, or purity beyond its official or established requirements.

**HUMAN DRUG CGMP NOTES, VOLUME 3, NUMBER 2**

(June, 1995)

Motise's Notebook

**POLICY QUESTIONS:**

2)

Reference: 21 CFR Sec. 211.65, Equipment construction, and Sec. 211.67, Equipment cleaning and maintenance.

Contact for Further Info: John Levchuck, HFD-322, 301-594-0095, e-mail: levchukj@fdacd.bitnet.

**ISPE Baseline Guide - Water and Steam Systems**

(First Edition, January 2001)

**2. KEY DESIGN PHILOSOPHIES**

**2.5 CGMP COMPLIANCE ISSUES**

2. Piping in WFI systems usually consist of a high polished stainless steel. In a few cases, manufacturers have begun to utilize PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems where low level metal contamination may accelerate the degradation of drug product, such as in the Biotech industry.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS**

(July, 1993)

**IX Piping**

(para 1)

[ViP ID: 987]

**"Piping in WFI systems usually consist of a high polished stainless steel. In a few cases, manufacturers have begun to utilize PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems where low level metal contamination may accelerate the degradation of drug product, such as in the Biotech industry."**

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## 5.6 Instrumentation

1. Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or recorders (e.g., a conductivity meter and recorder), manual documentation of operational parameters (such as carbon filter pressure drop) and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included.

**USP 26 - <1231> WATER FOR PHARMACEUTICAL PURPOSES Parts 01 - 03  
OPERATION, MAINTENANCE, AND CONTROL  
MONITORING PROGRAM  
[ViP ID: 2599]**

"Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or recorders (e.g., a conductivity meter and recorder), manual documentation of operational parameters (such as carbon filter pressure drop) and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included."

2. Typically, conductivity meters are used on water systems to monitor chemical quality and have no meaning regarding microbiological quality.

**REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS  
(July, 1993)  
V Still  
(para 5)  
[ViP ID: 977]**

"Typically, conductivity meters are used on water systems to monitor chemical quality and have no meaning regarding microbiological quality."

3. The following extract has been taken from the FDA's "Human Drug CGMP Notes", which is a memo issued to FDA personnel periodically to provide guidance on CGMP for human use pharmaceuticals.

***"What is the significance of the Total Organic Carbon (TOC) test for compendial processing waters (Purified Water, Water for Injection)?"***

Implicit in the term "Purified Water" is that it has some reasonable, objective level of purity. TOC testing allows for evaluating impurities in water besides those which are inorganic anions and cations.

Carbon-based (organic) compounds are often more complex than inorganic impurities. TOC allows for a quick, broad test for organic impurities. Numerous compounds can be detected under the umbrella of TOC, but it is important to be aware that this method is not capable of differentiating between specific organic compounds.

There is a long history of testing water for the presence of organic compounds. TOC's predecessor, oxidizable substances, is widely considered a less accurate, outdated test. As of May, 1998, TOC is the official organic impurities test for USP pharmaceutical processing waters."

**HUMAN DRUG CGMP NOTES, Volume 6, Number 4  
(December, 1998)**

**Motise's Notebook**

**POLICY QUESTIONS: Question 4**

**Reference: 21 CFR 211.80 General requirements [Subpart E-Control of Components and Drug Product Containers and Closures]; 211.84, Testing and approval or rejection of components, drug product containers, and closures**

**Contact for further information: Richard L. Friedman,  
HFD-322, 301-594-0095; e-mail: friedmanr@cderr.fda.gov**

**[ViP ID: 5983]**

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## 5.7 Biofilms

1. Organisms exist in a water system either as free floating in the water or attached to the walls of the pipes and tanks. When they are attached to the walls they are known as biofilm, which continuously slough off organisms. Thus, contamination is not uniformly distributed in a system and the sample may not be representative of the type and level of contamination. A count of 10 CFU/mL in one sample and 100 or even 1000 CFU/mL in a subsequent sample would not be unrealistic.

### REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

(July, 1993)

#### III MICROBIAL LIMITS

Purified Water Systems

(para 3)

[ViP ID: 967]

"Organisms exist in a water system either as free floating in the water or attached to the walls of the pipes and tanks. When they are attached to the walls they are known as biofilm, which continuously slough off organisms. Thus, contamination is not uniformly distributed in a system and the sample may not be representative of the type and level of contamination. A count of 10 CFU/mL in one sample and 100 or even 1000 CFU/mL in a subsequent sample would not be unrealistic."

## 5.8 System Sanitisation

1. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

### EU Guide to Good Manufacturing Practice: Annex 01 - Manufacture of Sterile Medicinal Products (September, 2003)

Equipment

35.

[ViP ID: 63280]

2. Another design consideration is the temperature of the system. It is recognised that hot (65 - 80°C) systems are self sanitising. While the cost of other systems may be less expensive for a company, the cost of maintenance, testing and potential problems may be greater than the cost of energy saved.

### REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

(July, 1993)

#### I SYSTEM DESIGN

(para 3)

[ViP ID: 949]

3. As an additional comment on RO systems, with the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75 - 80°C to minimise microbiological contamination.

### REG 07/01/93 GUIDE TO INSPECTIONS OF HIGH PURITY WATER SYSTEMS

(July, 1993)

#### X Reverse Osmosis

(para 3)

[ViP ID: 992]

"As an additional comment on RO systems, with the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75 - 80°C to minimize microbiological contamination."