USP 39 – S2

REVISIONS TO INFORMATIONAL CHAPTER <1231>

"WATER FOR PHARMACEUTICAL PURPOSES"

Joe Manfredi
GMP Systems, Inc.

THANKS TO T.C. SOLI, Ph.D.

Soli Pharma Solutions, Inc.

T. C. Soli, President, Consulting & Training Services since 2004 after 25 years in "big pharma"

USP Expert Committees

USP Chemical Analysis Expert Committee [Incl. Pharma Water] 2010-2020 (USP 34-43)

USP Pharmaceutical Water Expert Committee 2000-2010 (USP 24-33)

PhRMA Water Quality Committee

USP Advisory Council for USP 23 Water Changes 1989-2000

Prior <1231> Author

Current Contributing <1231> Author

Provided summary of <1231> changes, data, commentary and background details for this presentation

USP Disclaimer

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Opinions and analysis of this material are our own and not necessarily those of USP

Both TC and I are unpaid volunteers

Reasons for the revision

Satisfy User Needs & Address Questions:

- Issues needing clarification in <1231> (2006)
  - **Sampling**
  - **Biofilm**
  - **Process Control Alert and Action Levels**
  - **Quality Control Specifications**
  - **Chapter Organization & Structure**
  - **Microbial Test Methods**
  - **Objectionable Organisms**
  - **Microbiome & Likely/Unlikely Organisms**
  - **Validation**
  - **Source Water**
  - **Not mandatory* & not all encompassing**

USP 39, SUPPLEMENT 2 REVISIONS TO <1231>

New and improved text

- Much needed clarifications
- Added examples
- Added detail
- “Myth Buster”

<1231> FORMAT CHANGES

- Reorganized for user convenience
- Table of contents added
- Less redundancy
- More info and added clarity
- Contemporized with hyperlinks
- Dispels misconceptions

EXTENSIVE TABLE OF CONTENTS

1. INTRODUCTION
2. SOURCE WATER CONSIDERATIONS
3. WATERS USED FOR PHARMACEUTICAL MANUFACTURING AND TESTING PURPOSES
3.1 Bulk Monographed Waters and Steam
3.1.1 Purified Water
3.1.2 Water for Injection
3.1.3 Water for Hemodialysis
3.1.4 Pure Steam
3.2 Sterile Monographed Waters
3.2.1 Sterile Purified Water
3.2.2 Sterile Water for Injection
3.2.3 Bacteriostatic Water for Injection
3.2.4 Sterile Water for Irrigation
3.2.5 Sterile Water for Inhalation
3.3 Nonmonographed Waters
3.3.1 Drinking Water
3.3.2 Other Nonmonographed Waters
3.3.3 Ammonia-Free Water
3.3.4 Carbon Dioxide-Free Water
3.3.5 Distilled Water
3.3.6 Freshly Distilled Water
3.3.7 Deionized Water
3.3.8 Deionized Distilled Water
3.3.9 Filtered Water
3.3.10 High-Purity Water
3.3.11 Deaerated Water
3.3.12 Oxygen-Free Water
3.3.13 Water for Bacterial Endotoxins Test
4. VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS
4.1 Validation Requirement
4.2 Validation Approach
4.2.1 Validation Elements
4.2.2 User Requirements Specification and Design Qualification
4.2.3 IQ
4.2.4 OQ
4.2.5 PQ
4.3 Operational Use
4.3.1 Monitoring
4.3.2 Validation Maintenance
4.3.3 Change Control
4.3.4 Periodic Review
5. DESIGN AND OPERATION OF PURIFIED WATER AND WATER FOR INJECTION SYSTEMS
5.1 Unit Operations Considerations
5.1.1 Prefiltration
5.1.2 Activated Carbon
5.1.3 Additives
5.1.4 Organic Scavengers
5.1.5 Softeners
5.1.6 Deionization
5.1.7 Reverse Osmosis
5.1.8 Ultrafiltration
5.1.9 Microbial-Retentive Filtration
5.1.10 Ultraviolet Light
5.1.11 Distillation
5.1.12 Storage Tanks
5.1.13 Distribution Systems
5.1.14 Novel/Emerging Technologies
5.2 Installation, Materials of Construction, and Component Selection
5.3 Sanitization
5.3.1 Thermal Sanitization
5.3.2 Chemical Sanitization
5.3.3 UV Sanitization
5.3.4 Sanitization Procedures
5.4 Operation, Maintenance, and Control
5.4.1 Operating Procedures
5.4.2 Process Monitoring Program
5.4.3 Routine Microbial Control
5.4.4 Preventive Maintenance
5.4.5 Change Control
6. SAMPLING
6.1 Purposes and Procedures
6.1.1 PC Sampling
6.1.2 QC Sampling
6.2 Attributes and Sampling Locations
6.2.1 Chemical Attributes
6.2.2 Microbial Attributes
6.3 Validation Sampling Plans
6.4 Routine Sampling Plans
6.4.1 Source Water Sampling
6.4.2 Pretreatment and Purification System Sampling
6.4.3 Purified Water Distribution System Sampling
6.4.4 Water for Injection Distribution System Sampling
6.5 Non-Routine Sampling
7. CHEMICAL EVALUATIONS
7.1 Chemical Tests for Bulk Waters
7.2 Chemical Tests for Sterile Waters
8. MICROBIAL EVALUATIONS
8.1 Microorganism Types
8.1.1 Archaeans
8.1.2 Bacteria
8.1.2.1 Gram-Positive Bacteria
8.1.2.2 Gram-Negative Bacteria
8.1.2.3 Mycoplasma
8.1.3 Fungi
8.1.4 Viruses
8.1.5 Thermophiles
8.2 Biofilm Formation in Water Systems
8.2.1 Biofilm-Forming Bacteria in Water Systems
8.2.2 Non-Biofilm-Forming Bacteria in Water Systems
8.3 Microorganism Sources
8.3.1 Exogenous Contamination
8.3.2 Endogenous Contamination
8.4 Endotoxin
8.4.1 Sources
8.4.2 Removal and Control
8.5 Test Methods
8.5.1 Microbial Enumeration Considerations
8.5.2 The Classical Cultural Approach
8.5.2.1 Growth Media
8.5.2.2 Incubation Conditions
8.5.3 Suggested Classical Cultural Methods
8.5.4 Microbial Identification
8.5.5 Rapid Microbiological Methods
9. ALERT AND ACTION LEVELS AND SPECIFICATIONS
9.1 Introduction
9.2 Examples of Critical Parameter Measurements
9.3 Purpose of the Measurements
9.4 Defining Alert and Action Levels and Specifications
9.4.1 Alert Level
9.4.2 Action Level
9.4.3 Special Alert and Action Level Situations
9.4.4 Specifications
9.4.5 Source Water Control

Source Water

SOURCE WATER

If water supplied is from an unregulated source, user is required to verify compliance with all attributes of 1 of the 4 drinking water regulations cited (US, EU, WHO, Japan)

May require pre-pretreatment to comply

Source water quality may vary because of local environmental and seasonal changes

Frequency of compliance testing as needed to accommodate those seasonal changes

Importance of starting with Drinking Water

Required by GMP's for manufacturing and by USP for making PW and WFI

Allows non-specific chemical tests (Conductivity and TOC) to be used for finished waters

Allows compliance with Elemental Impurities <232> (reqd. 1/1/2018 !!!)

Water for Pharmaceutical Manufacturing & Testing

USP WATER MONOGRAPHS

Descriptions of methods of preparation and uses

- **Bulk monographed waters and steam**
  - Purified Water
    - **PW quality is minimum where "water" referenced in USP**
  - Water for Injection
  - Water for Hemodialysis
  - Pure Steam
- **Sterile monographed waters (possible quality issues based on container leachables)**
  - Sterile Purified Water
  - Sterile Water for Injection
  - Bacteriostatic Water for Injection
  - Sterile Water for Irrigation
  - Sterile Water for Inhalation

NON-MONOGRAPH WATERS

Non-monographed waters - with explanation (those mentioned > 1-2 times)

- **Drinking water**
- **Ammonia-free water**
- **Carbon-dioxide-free water**
- **Distilled water**
- **Freshly distilled water**
- **Deionized water**
- **Deionized distilled water**
- **Filtered water**
- **High-purity water**
- **Deaerated water**
- **Oxygen-free water**
- **Water for Bacterial Endotoxins Test**

USP WATER MONOGRAPHS

"…the monographed bulk and sterile waters have a statement indicating that there are no added substances, or no added antimicrobial agents. In the case of antimicrobial agents, the purpose is to ensure that the sterile water product is rendered sterile based solely on its preparation, packaging, and storage."

"In the case of the more general statement, "no added substances", this requirement is intended to mean "no added substances that aren't sufficiently removed"."

"It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as stated, are suitable for their intended use."

Validation

VALIDATION

Validation requirement

Document reliability of design, operation, maintenance, sanitization, monitoring, and use

Validation elements

URS and Design Qualification

- **Verify that the design meets the user requirement specifications**

Installation Qualification

- **Verify system is properly installed and intimately documented**

Operational Qualification

- **Verify unit performance, alarms, control sequences, Alert/Action Levels, SOPs**

Performance Qualification

- **Prospective Phase – Frequent monitoring, 2-4 weeks, no manufacturing**
- **Concurrent Phase – Less freq. monitoring, 2-4 weeks, manufacturing use at risk**

Routine Review

Periodic review of all routine monitoring and trending data, maintenance, Change Control to assure continuing control of validated state

Design & Operation

INSTALLATION & OPERATION

Installation, Materials of Construction, and Components

Avoid biofilm-promoting voids, crevices, & roughness
Assure; compatibility with good sanitizers, low leaching, durability

Sanitization

Thermal -- 65°C – 80°C is appropriate, > 80°C not beneficial, allow time for heat penetration if periodic, heat kills but doesn't remove biofilm
Treat often (or continuous) to avoid biofilm formation
Chemical (mostly oxidizers, difficulty with thick biofilm penetration – especially crevices, frequent use while biofilm still thin)
UV (planktonic kill only, flow rate critical, can protract needed period between sanitizations)

Operation, Maintenance and Control

Clear procedures and responsibilities, process and microbial monitoring program, preventive maintenance, change control, Unit Op discussions

INSTALLATION & OPERATION

"The critical difference *[between PW and WFI systems]* is the degree of control of the system and the final purification steps needed to ensure removal of bacteria and bacterial endotoxins and reductions in opportunities for biofilm re-development within those purification steps which could become *in situ* sources of bacteria and endotoxin in the finished water."

"Distillation coupled with suitable pretreatment technologies has a long history of generally reliable performance (though not completely infallible) and can be validated as a unit operation for the production of *Water for Injection*."

"Other combinations of purification technologies may also be suitable in the production of *Water for Injection* if they can be shown through validation to be as effective and reliable as distillation in the removal of chemicals and microorganisms."

Sampling

SAMPLING

Improper sample collection can lead to misinterpretation

- **No remediation when needed or remediation when not needed**
- **Product release errors (failed good product, passed bad product)**

Critical to understand purpose of sample and use correct, consistent procedure. How sample is removed from system affects its attributes

- **Process Control (PC) – Water quality within the system?**
  - Procedures to avoid contamination of flow path when removing water
  - Special valves, sterile hoses, vigorous flushing (≥ 8ft/s for 30s), sanitizers before and after use
  - Access unit operation performance (compendial or non-compendial)
- **Quality Control (QC) - Water quality delivered to point of use?**
  - Duplicate manufacturing use (and contamination by that use)
  - Same exact outlet, hose, outlet sanitization (if any), flushing (if any)
  - Accommodate hard-piped connections with same sampling philosophy
  - Where use practice is bad (high counts), improve use practice to allow good sampling practices and improved performance (good counts).

SAMPLING

Chemical attributes & sampling locations for distrib. system

Tend to be uniformly distributed unless localized contamination
On-line monitoring at loop return to see contaminants coming from POUs
Local sampling for localized contamination, e.g. TOC after heat exchanger

Microbial attributes & sampling locations for distrib. system

Not uniformly distributed, loop counts lower than outlets, some worse
On-line monitoring useful for PC but usually not for QC
Outlet counts greatly affected by how water is removed/used – so must use grab samples mimicking manufacturing use for QC

New ISPE Sampling GPG provides additional explanation and information

SAMPLING

"If improperly collected, a sample could yield a test result that is unrepresentative of the sample's purpose. This could lead to inaction when remediation is needed or to unnecessary remediation when none is necessary. It could also lead to misinterpretations of product impact."

"The data from water testing are generally used for one of two purposes: for process control (PC) of the water purification and distribution system or for quality control (QC) of the water being drawn from the system for some application or use."

"Because PC sampling is intended to reflect the quality of the water behind the valve … efforts should be made to avoid contaminating the water as it drawn from the system so that its test results accurately reflect the water quality within the system at that location."

"A fully open valve flush (at >8 ft/s velocity within the valve and connector) for at least 30 seconds typically provides sufficient shear forces to adequately remove any fragile biofilm structures."

"QC sampling is intended to reflect the quality of water that is being used. These samples should be collected at the true point of use, that is, where the water is delivered for use, not where it leaves the water system."

"The water delivery process and components used for QC sampling must be identical to manufacturing practices."

Chemical Evaluation

CHEMICAL TESTING

Chemical Tests for Bulk Waters

- **Replacement of wet chemistry tests with Conductivity and TOC**
- **Example of how conductivity limits derived**
- **Allows on-line instruments instead of lab testing of grab samples if on-line location qualified as representative, but both allowed**

Chemical Tests for Sterile Packaged Waters

- **Chemical tests primarily detect packaging leachables**
- **Graded conductivity limit depending on package size**
- **Traditionally-used Oxidizable Substances test insensitive to many organic leachables and allowed packages with high TOC**
- **Difficulty in setting TOC limit now with current packaging**
- **Sterile packaged waters not as pure as bulk water equivalent**
  - Be careful with lab and manufacturing applications to assure sterile packaged water works as well as bulk water equivalent

Microbial Evaluation

MICROBIAL CONTROL

Microorganism Types
- Discusses types of microorganisms and likelihood of colonizing high purity water systems

Biofilm Formation in Water Systems
- Discusses how biofilms form and which microorganisms do and don't form biofilms in water systems

Microorganism Sources
- Exogenous/Endogenous (outside/inside the water system)

Endotoxins
- Sources/Removal and Control

Test Methods
- Users responsibility to demonstrate method suitability for recovering microbiome in water system
- Test recovers only planktonic portion released from biofilm
- Classic Culture approaches with examples
- Identification & Objectionable Organisms
- Rapid Microbial Methods

MICROBIAL CONTROL

Excerpts

- **"Although Gram-positive bacteria can be detected in pharmaceutical water samples, their recovery is often associated with faulty aseptic technique during sampling or testing, or associated with exogenous contamination sources."**
- **"Gram-negative bacteria are of keen interest to pharmaceutical manufacturers…. Some Gram-negative bacteria prefer aquatic habitats and tend to colonize water systems as biofilms."**
- **"…the EPS matrix of biofilms is primarily responsible for the biofilm's success in … high-purity water systems. The EPS matrix also explains the difficulty in killing and/or removing biofilms from water purification and distribution system surfaces."**

MICROBIAL CONTROL

Excerpts

- **"Some of the biofilm pseudomonads are opportunistic human pathogens and may possess resistance to commonly used pharmaceutical product preservatives, particularly when imbedded in EPS matrix flocs sheared from water system biofilms."**
- **"Other types of non-pseudomonad Gram-negative bacteria are generally non-aquatic by nature. They include coliforms… *[which]* are extremely unlikely contaminants of pharmaceutical water systems.**
- **"Every water system has a unique microbiome. It is the user's responsibility to perform method validation studies to demonstrate the suitability of the chosen test media and incubation conditions for bioburden recovery. In general, users should select the method that recovers the highest planktonic microbial counts in the shortest time."**

MICROBIAL CONTROL

Establish control levels from trends (many ways)

Alert Level: at edge of normal variability

- **Could be single quantitative event**
- **Could be a non-zero event (hit) when norm is zero, regardless of size**

Action Level: above Alert but less than Specification

- **Could be single quantitative event or repeated alerts**
- **Could be recovery of objectionable organism**
- **Could be several non-zero hits when norm is zero**

Establish control levels as fractions of Specification

Make sure near normal levels and sufficiently below Specification to allow remediation before OOS

Control sampling to control data variability

MICROBIAL CONTROL

Water Quality Specifications

Intentionally NO Microbial Specifications in USP bulk water monographs

- **Rationale: necessary for most but not all applications, e.g.**
  - Vast majority of Lab analyses – but must verify/justify no microbial impact
  - Cleaning processes ending in heat/solvents which kill water bioburden
- **Unfair to require micro control and testing if irrelevant to use**

Specification created by user if not in monograph – in user documents

- **Based on user's product and process needs or tolerances**
- **FDA's expectation: No more than 100cfu/mL for Purified Water**
- **FDA's expectation: No more than 10cfu/100mL for WFI (200mL test)**

Specifications needed even if water already used before quality known

- **No different than any other raw material in formulations, except timing**
- **Fear of failing Pass/Fail Spec, OOS investigation, Product rejection**
- **Need for system control below Spec. by Alert/Action Levels, never close**
- **Control the sampling and water use SOPs to reduce data variability**

MICROBIAL CONTROL

"As *[process control]* indicators, Alert and Action Levels are trigger points for the potential need for investigation and/or remedial action, to prevent a system from deviating from normal conditions and producing water unsuitable for its intended use."

"This "intended use" minimum quality is sometimes referred to as a "Specification" or "Limit", and may include limits for conductivity and TOC listed in water monographs, or other specifications required for these waters that have been defined by the user internally *[e.g. bioburden].*"

"The resulting data must not be unduly biased, positively or negatively, due to the sampling method, the environment in the vicinity of the sampling location, the test procedure, instrumentation, or other artifacts that could obscure or misrepresent the true quality of the water intended by the purpose of the sampling, i.e., for PC or for QC."

General

Introduction

Importance of water in pharmaceutical manufacturing
Non-mandatory, informational chapter
Summary of chapter topic content
Not an all-inclusive water text
User responsibilities to:

- **Use correct water for application**
- **Have appropriate chemical/endotoxin/microbial controls**
  - Microbial specifications intentionally not in some USP monographs
- **Meet water quality needs of application**
- **Be compliant with all compendial/governmental regulations**

"This informational chapter is intended to be educational, and the user should also refer to existing regulations or guidelines that cover U.S. and international good manufacturing practice (GMP) issues, as well as operational and engineering guides and/or other regulatory guidance for water…"
"This chapter is not, and should not be considered, an all-inclusive document on pharmaceutical waters."
"Attributes listed in *USP* monographs should be considered the *minimum* requirements. More stringent requirements may be needed for some applications to ensure suitability for particular uses."

Summary

CHAPTER <1231> SUMMARY

Importance of water in pharmaceutical manufacturing

Non-mandatory, informational chapter

Summary of chapter topic content

Not an all-inclusive water text
- Need to refer to other engineering and governmental guides / regs.

User responsible to:
- **Use correct water for application**
- **Have appropriate chemical/endotoxin/microbial controls**
  - Microbial specifications intentionally not in some USP monographs
- **Meet water quality needs of application**
  - Compendial requirements are minimum expectations, purer may be needed
- **Be compliant with all compendial/governmental regulations**

More changes expected in the future!

Thanks !!!

Questions?

Please use the microphone indicated so our recording includes audio of your question

For further information, please contact:

Joseph Manfredi
GMP Systems, Inc.
14 Madison Rd.
Suite F
Fairfield, NJ 07004
973-575-5990 office
jmanfredi@gmpsystems.com

T. C. Soli
Soli Pharma Solutions
15112 Pleasant Valley Rd.
Woodstock, IL 60098
815-451-8965 or 8801 office
252-902-5097 mobile
tcsoli@earthlink.net