Compounding Pharmacies and Water

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Disclaimer

• I am an independent consultant.
• I have been involved with USP for many years.
• I do not represent USP or any other organization.
• Opinions expressed in this webinar are mine alone, and should not be interpreted as the policies, positions or whims of any other organization.
Presentation Overview

• Water and Compounding – What’s in it for me?
• Water and USP
  • <797>
  • <1231>
  • Monographs
• Water, Compounding and FDA
• Summary

Water is Used

• CSP
  • Sterile Water for injection
  • Sterile Water for irrigation
  • Sterile Bacteriostatic Water for injection
• Non-sterile
  • Water for Injection
  • Purified Water
• Potable Water
Water is Used

- Cleaning of Product-contact Equipment
  - Primary cleaner
  - Rinses
- Cleaning of Facility
- Cleaning of hands

Water is an Issue

- Promotes microbial growth
- Is itself a source of microbial contamination
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USP <797>

“All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding.”
Multiple references to handwashing and technique

Quality of water to use when making media for process simulations

Cleaning and Disinfecting the Compounding Area

“Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned and surfaces shall be cleaned by removing loose material and residue from spills, e.g., water-soluble solid residues are removed with Sterile Water (for Injection or Irrigation) and low-shedding wipes.”
Abbreviated History of Water in USP

1820  Aqua Fontana and Distilled Water
1840  First testing requirements
1850, 1880, 1890, 1900  Tests Added
1910  Sterile distilled water
1942  Water for Injections
1955  Purified Water
1970  Information Chapter <1231> on “Water for Pharmaceutical Purposes”
1996  TOC and Conductivity
2003, 2005, 2010  Increase in information provided, more microbiology in <1231>
2014  Changes to promote harmonization with Pharm Eur; New waters

<1231> Water for Pharmaceutical Purposes

- Introduction
- Source or Feed Water Considerations
- Types of Water
- Validation and Qualification of Water Purification, Storage, and Distribution Systems
- Purified Water and Water for Injection Systems
- Unit Operations Concerns
- Installation, Materials of Construction, and Component Selection
- Sanitization
### Water for Pharmaceutical Purposes (cont)

- Operation, Maintenance, and Control
- Sampling Considerations
- Chemical Considerations
- Microbial Considerations
- Endotoxin Considerations
- Microbial Enumeration Considerations
- Identification of Microorganisms
- Alert And Action Levels and Specifications

#### <1231>: Operation, Maintenance, and Control (OMC)

“A preventative maintenance program should be established to ensure that the water system remains in a state of control”

- Operating Procedures
- Monitoring Program
- Sanitization
- Preventative Maintenance
- Change Control
<1231> OMC - Operating Procedures

• Operation of equipment
• Performing routine maintenance
• Should be written
• Define point at which action is required
• Well documented
• Detail function, identity and procedures of each job
• Effectiveness of procedures established during system validation

<1231> OMC - Monitoring Program

• Critical quality attributes and operating parameters should be documented and monitored
• May be combination of in-line sensors, manual records and lab tests
• Frequency of testing should be defined
• Requirement to evaluate test results
• Need to initiate corrective action should be defined
<1231> OMC - Sanitization

- May include clean-in-place
- May include hot loop (~80°C)
- May include
  - UV
  - Filter
  - Others

<1231> OMC – Preventative Maintenance

- PM Program should be in effect
- Required maintenance should be detailed
- Frequency of maintenance activities described
- How to document the work
<1231> OMC – Change Control

- Water system configuration and operating conditions must be controlled
- Proposed changes must be evaluated for effect on whole system
- Need to requalify whole system after changes must be evaluated
- Schematics of water system must be kept current

Microbial Considerations

- Major source of contamination is the source water
- Unit operations a prime concern
  - Biofilm may form on carbon beds, filters, etc
- Distribution System
  - Dead-legs, valves, walls
- Endotoxins
Microbial Considerations

- Identification of Microorganisms
  - Recommended

- Alert and Action Levels
  - Alert Level: process drifting from normal operation condition if exceeded
  - Action Level: process drifting from normal operating range, if exceeded
  - Corrective Action even when product quality might not be compromised

Water Quality as Defined by USP

1. Total Organic Carbon
2. Conductivity
3. Bioburden
4. Endotoxin
5. Sterility
6. Antimicrobial Efficacy
USP TOC Test Method <643>

• USP chapter provides method to monitor Total Organic Carbon
• Purpose
  • Organic matter can get into water from
    • Living organisms
    • Decaying matter in source water
    • Materials in purification distribution systems
  • Monitoring water for low TOC provides documentation of control
  • TOC levels are also used to monitor success of water system sanitization programs

Conductivity Test – USP <645>

• Test method is provided in USP <645>
• Purpose
  • Conductivity is a measure of the ability of water to pass an electrical current.
  • Affected by the presence of inorganic dissolved solids such as
    • chloride, nitrate, sulfate, and phosphate anions (ions that carry a negative charge)
    • sodium, magnesium, calcium, iron aluminum cations (ions that carry a positive charge).
    • Organic compounds like oil, phenol, alcohol, and sugar do not conduct electrical current very well and therefore have a low conductivity when in water.
Microbiological Specs

Recommendations in USP Monographs and <1231>

- Bioburden
- Sterility
- Endotoxin
- Bacteriostasis

Water Monographs

- Water for Injection
  - Sterile
  - Bacteriostatic
- Sterile Water for Irrigation
- Sterile Water for Inhalation
- Pure Steam
- Purified Water; Sterile Purified Water
Water Requirements

<table>
<thead>
<tr>
<th>Monograph</th>
<th>TOC</th>
<th>Conductivity</th>
<th>Bioburden</th>
<th>Endotoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water for Injection</td>
<td>NMT 0.50 mg/mL</td>
<td>NMT 2.1 µS/cm</td>
<td>10 CFU/100 mL</td>
<td>&lt;0.25 EU/mL</td>
</tr>
<tr>
<td>Sterile Water for Irrigation</td>
<td>NMT 0.50 mg/mL</td>
<td>NMT 2.1 µS/cm</td>
<td>Meets Sterility Test Req</td>
<td>&lt;0.25 EU/mL</td>
</tr>
<tr>
<td>Sterile Water for Inhalation</td>
<td>NMT 0.50 mg/mL</td>
<td>NMT 2.1 µS/cm</td>
<td>Meets Sterility Test Req</td>
<td>&lt;0.5 EU/mL</td>
</tr>
<tr>
<td>Pure Steam</td>
<td>NMT 0.50 mg/mL</td>
<td>NMT 2.1 µS/cm</td>
<td>--</td>
<td>&lt;0.25 EU/mL</td>
</tr>
<tr>
<td>Purified Water</td>
<td>NMT 0.50 mg/mL</td>
<td>NMT 2.1 µS/cm</td>
<td>100 CFU/mL</td>
<td>--</td>
</tr>
<tr>
<td>Potable Water</td>
<td>--</td>
<td>--</td>
<td>500 CFU/mL</td>
<td>--</td>
</tr>
</tbody>
</table>

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FDA Concerns

- Appropriate use of water (quality for purpose)
- Water used for hand-washing
- Pools of water/water leaks in pharmacy

Water Used for Handwashing

There were several observations to different pharmacies on inappropriate handwashing facilities, especially entering the aseptic area.

- Elbow faucets
- Foot faucets
Note for Guidance on Quality of Water for Pharmaceutical Use - CPMP/QWP/158/01; May 2002

Quality of Water for Pharmaceutical Use

- Sterile Medicinal Products
- Non-sterile Medicinal Products
- Water used during the manufacture of Active Pharmaceutical Ingredients
- Water used during Manufacture of Medicinal Products Which is Not Present in the Final Product
- Water Used for Cleaning/Rinsing of Equipment, Containers and Closures
### NfG on Quality of Water for Pharmaceutical Use

#### Water as an excipient - Steriles

<table>
<thead>
<tr>
<th>Product</th>
<th>Minimum Acceptable Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral</td>
<td>WFI</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Purified</td>
</tr>
<tr>
<td>Haemofiltration Solutions</td>
<td>WFI</td>
</tr>
<tr>
<td>Haemodiafiltration Solutions</td>
<td>WFI</td>
</tr>
<tr>
<td>Peritoneal Dialysis Solutions</td>
<td>WFI</td>
</tr>
<tr>
<td>Irrigation Solutions</td>
<td>WFI</td>
</tr>
<tr>
<td>Nasal/Ear Solutions</td>
<td>Purified</td>
</tr>
<tr>
<td>Cutaneous Preparations</td>
<td>Purified</td>
</tr>
</tbody>
</table>

#### Water as an excipient - Non-steriles

<table>
<thead>
<tr>
<th>Product</th>
<th>Minimum Acceptable Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Preparations</td>
<td>Purified</td>
</tr>
<tr>
<td>Nebuliser Solutions</td>
<td>Purified*</td>
</tr>
<tr>
<td>Cutaneous Preparations</td>
<td>Purified</td>
</tr>
<tr>
<td>Nasal/Ear Solutions</td>
<td>Purified</td>
</tr>
<tr>
<td>Rectal/Vaginal Preparations</td>
<td>Purified</td>
</tr>
</tbody>
</table>

* Except for those required to be sterile and non-pyrogenic (e.g. cystic fibrosis) where WFI should be used.
### NfG on Quality of Water for Pharmaceutical Use

**Water used during manufacture of medicinal products which is not present in the final formulation**

<table>
<thead>
<tr>
<th>Manufacture</th>
<th>Minimum Acceptable Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulation</td>
<td>Purified*</td>
</tr>
<tr>
<td>Tablet Coating</td>
<td>Purified</td>
</tr>
<tr>
<td>Used in formulation prior to non-sterile lyophilisation</td>
<td>Purified</td>
</tr>
<tr>
<td>Used in formulation prior to sterile lyophilisation</td>
<td>WFI</td>
</tr>
</tbody>
</table>

* Potable water may be acceptable for some veterinary premix products (granulated concentrates) if justifiable by chemical and microbiological quality.

### NfG on Quality of Water for Pharmaceutical Use

<table>
<thead>
<tr>
<th>Cleaning/Rinsing of Equip., Containers, Closures</th>
<th>Product Type</th>
<th>Min. Acceptable Quality of Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Rinse</td>
<td>Intermediates and API</td>
<td>Same Quality as in API manufacture</td>
</tr>
<tr>
<td>Final Rinse</td>
<td>API</td>
<td>Potable Water</td>
</tr>
<tr>
<td>Initial Rinse Including CIP</td>
<td>Non-sterile Products</td>
<td>Purified Water</td>
</tr>
<tr>
<td>Final Rinse Including CIP</td>
<td>Non-sterile Products</td>
<td>Purified Water</td>
</tr>
<tr>
<td>Initial Rinse Including CIP</td>
<td>Sterile non-parenteral Products</td>
<td></td>
</tr>
<tr>
<td>Final Rinse Including CIP</td>
<td>Sterile non-parenteral Products</td>
<td></td>
</tr>
<tr>
<td>Final Rinse Including CIP</td>
<td>Sterile parenteral Products</td>
<td>WFI</td>
</tr>
<tr>
<td>Final Rinse Including CIP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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483 from Pharmacy 7/26/13

g) Your firm uses an in-house purified water system to wash vials and stoppers before they are sterilized and used to fill sterile drug products. However, your firm could not provide any scientific data to confirm that the water system is monitored, sampled and maintained on a schedule that demonstrates the water is not adding additional bioburden to the containers and closures prior to in-house sterilization and depyrogenation. In addition, your firm's formula worksheet that is printed as a batch record for the washing, sterilization and depyrogenation of the vials specifies “all clean glassware and serum vials are rinsed with purified water.” There is no data to demonstrate the water meets the specifications of “purified” water.

FDA 483 Issued 7/21/14

OBSERVATION 5

The control systems necessary to prevent contamination or mix-ups are deficient.

(?) The firm's Class 10,000 clean room has a sink with faucets for municipal tap water and "purified" water and a drain open to the environment approximately three feet to the side of the ISO 5 vertical flow biosafety hood that it sometimes uses to process sterile human and animal drug products prior to sterilization.
FDA 483 Issued 7/21/14

OBSERVATION 8

Equipment and utensils are not cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

(a) The firm rinses sterilized glass beakers and stir bars used to produce bulk product solutions with "purified water". This water is produced at room temperature from municipal tap water in a stagnant system consisting of [redacted]. The firm has not tested the water to determine its purity, bioburden, or pyrogen levels.

FDA 483 9/10/13

OBSERVATION 4

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically, tap water (sink in the ISO-8 ante room is filtered via the use of a [redacted] faucet filter) is used to wash personnel hands and arms as well as to clean and wash amber color vials that are used for aseptically filled sterile drug commodities. The filter manufacturer submits that the "faucet filtration system is not intended to purify water". Furthermore, the faucet system is not designed, or intended, for the removal and/or retention of bacterial endotoxin. When asked if the [redacted] faucet filter was periodically removed and replaced, the technician explained that she believed the filter is replaced however there is no record to document the practice.
FDA 483 Issued 3/8/2013

a) Your firm clean equipment and utensils, including glass beakers used to process drug products prior to sterilization, by hand-washing in a sink with household dish detergent and then in a household style dishwasher using household dish washer detergent. The water supplied to the sink and dishwasher are municipal source and is not further treated. Your firm has no evidence that this cleaning method is appropriate for equipment and utensils used to produce sterile drug products.

FDA 483 Issued 2/25/13

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not.

b) The [redacted] water system located in the ISO 8 Prep room supplies water to the firm's [redacted]. There is no written SOP outlining the use and maintenance of the water system. The water system is maintained [redacted] by an outside contractor. In addition, the firm does not perform conduct any sampling and testing of the water quality produced by the [redacted] water system.

Pharmacy later 503B registered
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QUESTIONS?

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Consulting
- Contamination Control/Sterility Assurance
- Quality Assurance
- Quality Control
  - Microbiology Lab Operations/Design/Audits
  - Microbiology Process/Procedure
  - Product Development

Turn-key Projects
We will supply national expert supervision and/or bench-level assistance for short term or long-term needs (facility qualification, laboratory creation/expansion)

Training
- In-house Training
- Distance (web-based) training
  - Next Compounding Webinar – Sept 18 - Compounding Pharmacies and Personnel Controls
  - Custom webinar training

Thank you for your attention
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