Welcome

Empowering a healthy tomorrow
USP Perspective on Pharmaceutical Waters

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Why is Water Important?

- Raw material
- Solvent
- Ingredient
- Reagent
- Cleaning agent (hot water or steam)

- Sterile waters
  - Sterile Water for Irrigation
  - Sterile Water for Inhalation
  - Sterile Purified Water
  - Bacteriostatic Water for Injection
  - Water for Hemodialysis

- Packaged waters
  - Purified Water for small volume use
Identity, Strength, Purity

- How do you "identify" water?
  - Molecular weight 18.02
  - Chemical structure

- Strength
  - ?

- How do you characterize its purity?
  - Microbiological
  - Organic (non-living)
  - Inorganic
  - Particulate
  - Dissolved Gases
<table>
<thead>
<tr>
<th>Impurity Types</th>
<th>Characteristics</th>
<th>Types of Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological</td>
<td>living, organic</td>
<td>sterility</td>
</tr>
<tr>
<td>Microbiological</td>
<td>dead, organic</td>
<td>BET</td>
</tr>
<tr>
<td>Organic</td>
<td>non-ionic</td>
<td>TOC</td>
</tr>
<tr>
<td>Inorganic</td>
<td>ionic</td>
<td>conductivity</td>
</tr>
<tr>
<td>Particulate</td>
<td>insoluble</td>
<td>filter/particle counter</td>
</tr>
<tr>
<td>Dissolved Gases</td>
<td>ionic, non-ionic</td>
<td>usually benign</td>
</tr>
</tbody>
</table>
PHARMACEUTICAL WATER PREPARATION
Pharmaceutical Water Preparation

**Pretreatment**
- Primary filtration
- Hardness reduction
- Disinfectant removal
- Pre-filtration
- Bacteria reduction

**Purification**
- Primary purification
- Polishing
- Bacteria reduction (optional)
- Final purification (optional)

**Points of Use (POU)**

Feed Water → Pharmaceutical Water → Points of Use (POU)
Possible Pretreatment Methods

- Cartridge filter (5-20 μ)
- Multi-media filter

- Softener
- Anti-scalant

- Granular Activated Carbon (GAC) filtration
- Bisulfite injection
- pH adjust

- Cartridge filter (1-5 μ)

- Ultraviolet (UV) light
Possible Purification Methods

**Pretreatment**

- Reverse Osmosis (RO)
- 2 pass RO
- 3 pass RO

**Purification**

- Ion-exchange (DI)
- Mixed Bed DI
- EDI

- UV light
- Heat
- Chemical sanitize
- Ozone
- UF

**Final Purification**

- DI/EDI
- RO
- UF
- Distillation

**Storage & Distribution**

Pharmaceutical Water
Example - Pharmaceutical Water Preparation

**Pretreatment**
- Multi-Media Filter
- Cartridge Filter (5-20μ)
- Softener
- GAC
- Break Tank
- Cartridge Filter (1-5μ)
- UV

**Purification**
- RO Unit
- UF Unit
- CEDI
- UV
- Distillation for WFI
- Storage tank

**Storage & Distribution**
- Points of Use

For Reference only
## Classes of Contaminants/Removal Methods

<table>
<thead>
<tr>
<th>Type Process</th>
<th>Dissolved Ionic Solids</th>
<th>Dissolved Ionic Gases</th>
<th>Dissolved Organics</th>
<th>Particulates</th>
<th>Bacteria</th>
<th>Pyrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration micron</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>E</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Filtration sub-micron</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>E</td>
<td>E</td>
<td>P</td>
</tr>
<tr>
<td>Filtration ultra/nano</td>
<td>P</td>
<td>P</td>
<td>G</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Softener</td>
<td>E/G</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Carbon Adsorption</td>
<td>P</td>
<td>P</td>
<td>E/G</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Reverse Osmosis</td>
<td>G/E</td>
<td>P</td>
<td>G/E</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Deionization</td>
<td>E</td>
<td>E</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Distillation</td>
<td>E</td>
<td>P/E</td>
<td>G/E</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>UV Oxidation</td>
<td>P</td>
<td>P</td>
<td>G/E</td>
<td>P</td>
<td>G</td>
<td>P</td>
</tr>
</tbody>
</table>

E = Excellent, capable of complete or near total removal of impurity type  
G = Good, capable of removal of large %  
P = Poor, little or no removal
WATER MONOGRAPHS
The Pharmaceutical Waters Tree

Drinking Water

Purified Water

Sterile Purified Water

Sterile Water for Injection

Sterile Water for Inhalation

Sterile Water for Irrigation

Bacteriostatic Water for Injection

Water for Injection

Pure Steam

Water for Hemodialysis
## Bulk Purified Water - Today

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Production Method</strong></td>
<td>Suitable process</td>
<td>Suitable process</td>
<td>Distillation, ion-exchange, UF, or combination</td>
</tr>
<tr>
<td><strong>Source Water</strong></td>
<td>US, EU, Japan, WHO drinking water</td>
<td>Human consumption</td>
<td>JP water specification</td>
</tr>
<tr>
<td><strong>Total Aerobic (cfu/mL)</strong>^2</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td><strong>Conductivity (µS/cm at 25°C)</strong>^3</td>
<td>1.3 (3 stage)</td>
<td>5.1 (1 stage)</td>
<td>1.3 (3 stage)</td>
</tr>
<tr>
<td><strong>TOC (mg/L)</strong></td>
<td>0.5</td>
<td>0.5 (optional)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Bacterial Endotoxins (EU/mL)</strong></td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Nitrates (ppm)</strong></td>
<td>0.2</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Heavy Metals (ppm)</strong></td>
<td>0.1[^5]</td>
<td>Test with color indicators</td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Acidity/Alkalinity</strong></td>
<td></td>
<td></td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Chloride</strong></td>
<td></td>
<td></td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Sulfate</strong></td>
<td></td>
<td></td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Nitrite</strong></td>
<td></td>
<td></td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Ammonium (mg/mL)</strong></td>
<td></td>
<td></td>
<td>Not detectable</td>
</tr>
<tr>
<td><strong>Oxidizable Substances (/100 mL)</strong></td>
<td>&lt;0.1 mL[^4] 0.02 KMnO₄</td>
<td>&lt; 0.10 mL 0.02 KMnO₄</td>
<td>&lt; 0.10 mL 0.02 KMnO₄</td>
</tr>
<tr>
<td><strong>Residue on Evaporation (mg)</strong></td>
<td>1.0/100 mL</td>
<td></td>
<td>1.0/100 mL</td>
</tr>
</tbody>
</table>

**Note 1:** All tests are maximum, unless otherwise stated.

**Note 2:** Microbiological testing is not considered to be harmonized. The EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter.

**Note 3:** Limits are temperature dependent.

**Note 4:** Alternative to TOC.

**Note 5:** Not required effective Jan 1, 2009 if WFI conductivity requirements are met.

**Note 6:** Shaded chemical tests are deleted effective in JP16 (4/1/11).
### Bulk Water for Injection(s) - Today

<table>
<thead>
<tr>
<th>Attribute</th>
<th>USP 40</th>
<th>EP 9.3</th>
<th>JP 16&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Production Method</strong></td>
<td>Distillation or suitable process</td>
<td>Distillation</td>
<td>Distillation, RO with UF, from Purified Water</td>
</tr>
<tr>
<td><strong>Source Water</strong></td>
<td>US, EU, Japan, WHO DW</td>
<td>Human consumption</td>
<td>JP water specification</td>
</tr>
<tr>
<td>Total Aerobic (cfu/100 mL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Conductivity (µS/cm at 25°C)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1.3 (3 stage)</td>
<td>1.3 (3 stage)</td>
<td>1.3 (3 stage)</td>
</tr>
<tr>
<td>TOC (mg/L)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5 (0.3 for control)</td>
</tr>
<tr>
<td>Bacterial Endotoxins (EU/mL)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Nitrates (ppm)</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Heavy Metals (ppm)</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Acidity/Alkalinity</td>
<td>Test with color indicators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Nitrite</td>
<td>Not detectable</td>
<td>Not detectable</td>
<td>Not detectable</td>
</tr>
<tr>
<td>Ammonium (mg/mL)</td>
<td>0.5</td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Oxidizable Substances (/100 mL)</td>
<td>&lt; 0.10 mL 0.02 KMnO&lt;sub&gt;4&lt;/sub&gt;</td>
<td></td>
<td>&lt;0.10 mL 0.02 KMnO&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>Residue on Evaporation (mg)</td>
<td>1.0/100 mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **Note 1:** All tests are maximum, unless otherwise stated.
- **Note 2:** Microbiological testing is not considered to be harmonized. The EP test is written into the Production section, and the USP test is contained in a non-compendial general information chapter.
- **Note 3:** Limits are temperature dependent.
- **Note 4:** Not required effective Jan 1, 2009.
- **Note 5:** Shaded chemical tests are deleted effective in JP16 (1/1/11).
WFI – Method of Production

- **Purified Water**
  - USP, EP, JP permit any technology

- **Water for Injection**
  - USP permits “distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals or microorganisms”\textsuperscript{USP27}
  - EP permits distillation only
  - JP permits distillation or RO/UF

- **Highly Purified Water**
  - EP only, produced by RO, meets WFI
SCOPE

This paper outlines why it is currently not considered acceptable to use reverse osmosis for the production of water for injections (WFI).

In view of recent technological advancements in this field, this paper aims to stimulate discussion on this topic.

INTRODUCTION

Today the use of reverse-osmosis to prepare WFI is considered acceptable by the US Pharmacopoeia, however stringent requirements regarding validation and maintenance are required by the US FDA.

The European Pharmacopoeia requires that WFI must be prepared by distillation. Reverse osmosis is not considered acceptable in the EEA according to the recommendations of the Note for Guidance on Quality of Water for Pharmaceutical Purposes (CPMP/QWP/158/01 - EMEA/CVMP/115/01).

Considering economical and practical industrial aspects, it is often claimed that this technological approach should be accepted by EEA Competent Authorities. The major objections concern range of separation for reverse osmosis, validation and maintenance of devices and microbiological aspects.

CONCLUSION

Today it is not possible to assume that the quality of WFI prepared by reverse-osmosis is as safe as water prepared by distillation according to the requirement of the European Pharmacopoeia.
EMEA is re-opening discussion about use of alternative methods to product WFI.

The use of reverse osmosis in the preparation of water for injection has been discussed over the past years. Following exchanges with the European Medicines Agency (EMEA), the Commission has decided to organise a workshop with all stakeholders to establish a clear view of the state of the technology and to decide whether to integrate this method into the authorised list of methods to prepare water for injection.
USP – ISPE Survey

- USP develops a survey to acquire industry data
  - Water systems that meet requirements for WFI or other endotoxin-controlled waters
  - Considers pre-treatment, generation, distribution
  - Considers sanitation type and frequency
  - Considers a SYSTEM approach to making this water, not the RO.

- USP has partnered with ISPE/Critical Utilities Community of Practice (CU COP)
  - Survey delivered to CU COP June 2010.
  - Results reviewed in 2011
WATER MONOGRAPHS AND GENERAL CHAPTERS (RECENT CHANGES)
Updating Sterile Packaged Water Attributes: Conductivity and Total Organic Carbon

Anthony C. Bevilacqua, Lucia Clontz, Max S. Lazar, Bruno Rossi, Rostyslaw Slabicky, Teri C. Soli, Antonio Hernandez-Cardoso

ABSTRACT The Pharmaceutical Waters Expert Committee in the Council of Experts continues to update monographs for pharmaceutical waters. The next phase is to replace the Oxidizable Substances test for existing sterile water monographs with General Chapter Total Organic Carbon (TOC) 〈643〉 for packaged water. This initiative is aligned with harmonization discussions regarding the monograph for Sterile Water for Injection. A proposed TOC test for Sterile Water for Injection is based on the container size: not more than 1.00 mg of carbon per L for containers that have a fill volume greater than 10 mL and not more than 1.50 mg of carbon per L for containers that have a fill volume of 10 mL or less. The TOC test would be phased in by providing it as an alternative to Oxidizable Substances. The Oxidizable Substances test would be deleted approximately two years after the TOC test is official. Also proposed are Water Conductivity levels of 15 μS/cm for containers with a nominal volume of less than 10 mL and 5 μS/cm for containers with a nominal volume greater than 10 mL.
Determination of Organic Carbon Contamination in Packaged Pharmaceutical Water—Contributions by the Container

Yuriy O. Slabicky, Antonio Hernandez-Cardoso

ABSTRACT The Total Organic Carbon (TOC) concentrations in commercially available packages of Sterile Purified Water, Sterile Water for Injection, Sterile Water for Inhalation, and Sterile Water for Irrigation were surveyed to assist the USP Pharmaceutical Waters Expert Committee with the replacement of the Oxidizable Substances monograph test with a TOC test. The TOC was determined for waters in different glass and plastic containers. The average TOC concentration for the different pharmaceutical waters ranged from 329 μg of carbon per L to 5218 μg of carbon per L. The organic carbon contribution to the TOC was primarily from the packaging materials. The organic carbon contribution per container surface area was highest for packages made of flexible polyvinyl chloride (9.6 μg of carbon per cm²) and lowest for glass vials with elastomeric stoppers (0.27 μg of carbon per cm²).
BRIEFING

〈643〉 Total Organic Carbon, USP 35 page 266. It is proposed to revise this chapter to add a Total Organic Carbon limit test, to be used in the USP monographs Sterile Water for Injection, Sterile Purified Water, Sterile Water for Irrigation, and Sterile Water for Inhalation. The limit is proposed at 8.0 mg/L (8 ppm) of carbon, and it is based on a survey of the industry’s current capability for sterile products. This test will be an alternative to the Oxidizable Substances test, as described in concurrent proposed revisions to the water monographs cited above. For details, see these four proposed revised monographs in the section In-Process Revision in this issue of PF.

(GCPA: A. Hernandez-Cardoso.)
Correspondence Number—C115368

Comment deadline: July 31, 2012
EP 2.2.44 Total Organic Carbon

The method is identical to USP method FOR BULK WATERS.
4.5.2. Monitoring of TOC as the Indicator for Organic Impurities

The acceptance criterion of TOC is specified as “not greater than 0.50 mg/L (500 ppb)” in the monographs of *Purified Water and Water for Injection*. However, it is recommended for each facility preparing pharmaceutical water to conduct operation control of pharmaceutical water processing system through TOC monitoring on produced water based on its own alert and action levels for TOC determined individually. The following are the recommended action levels for TOC.

- Action Level:
  - ≤ 300 ppb (in-line)
  - ≤ 400 ppb (off-line)

The JP specifies the *Test for Total Organic Carbon <2.59>*

and normally, TOC measurement should be conducted using an apparatus which meets the requirements described in the JP method. However, if a TOC apparatus conforms to the apparatus suitability test requirements described in “<643> TOTAL ORGANIC CARBON” of the USP, or those described in the “Methods of Analysis 2.2.44. TOTAL ORGANIC CARBON IN WATER FOR PHARMACEUTICAL USE” of the European Pharmacopoeia (EP), the apparatus can be used for the monitoring of pharmaceutical water processing system, if sufficiently pure water not contaminated with ionic organic substances, or organic substances having nitrogen, sulfur, phosphorus or halogen atoms in their structures, is used as the source water supplied to the system.
**BRIEFING**

*Sterile Water for Injection*, USP 38 page 5806. In *PF 38(3) [May–June 2012]*, four sterile water monographs, including *Sterile Water for Injection*, were proposed to be updated. At the time, an Oxidizable Substances test was required. The change was to allow a Total Organic Carbon test as an alternative to the Oxidizable Substances test. The change became official in the First Supplement to USP 36. In the briefing of the same *PF* article, it was proposed to delete the Oxidizable Substances test in 18–24 months. This revision proposal deletes the option of the Oxidizable Substances test, and retains the Total Organic Carbon test that is specific to sterile waters.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

(GCCA: A. Hernandez-Cardoso.)
Correspondence Number—C157681

**Comment deadline:** July 31, 2015
Water Conductivity

Change to read:

INTRODUCTION

Electrical conductivity in water is a measure of the ion-facilitated electron flow through it. Water molecules dissociate into ions as a function of pH and temperature and result in a very predictable conductivity. Some gases, most notably carbon dioxide, readily dissolve in water and interact to form ions, which predictably affect conductivity. For the purpose of this discussion, these ions and their resulting conductivity can be considered intrinsic to the water.

Water conductivity is also affected by the presence of extraneous ions. The extraneous ions used in modeling the conductivity specifications described below are the chloride and ammonia ions. The conductivity of the ubiquitous chloride ion (at the theoretical endpoint concentration of 0.47 ppm when chloride was a required attribute test in USP 22 and earlier revisions) and the ammonium ion (at the limit of 0.3 ppm) represents a major portion of the allowed water ionic impurity level. A balancing quantity of anions (such as chloride, to counter the ammonium ion) and cations (such as sodium, to counter the chloride ion) is included in this allowed impurity level to maintain electroneutrality. Extraneous ions such as these may have a significant effect on the water's chemical purity and suitability for use in pharmaceutical applications.

The procedure in the section Bulk Water is specified for measuring the conductivity of waters such as Purified Water, Water for Injection, Water for Hemodialysis, and the condensate of Pure Steam. The procedure in the section Sterile Water is specified for measuring the conductivity of waters such as Sterile Purified Water, Sterile Water for Injection, Sterile Water for Inhalation, and Sterile Water for Irrigation.
BRIEFING

1644 Theory and Practice of Electrical Conductivity Measurements of Solutions. There is a growing use of electrical conductivity measurements of fluids in pharmaceutical processes, and there is a void in the USP general chapters of information regarding the use of this analytical tool. There are some texts and articles related, including from NIST, which could be used as references for interested users. This new chapter provides general information on the use, application theory of operation, terminology, calibration, and performance of electrical conductivity measurement of fluids.

(GCCA: A. Hernandez-Cardoso.)
Correspondence Number—C98558

Comment deadline: July 31, 2011

Add the following:

1644 THEORY AND PRACTICE OF ELECTRICAL CONDUCTIVITY MEASUREMENTS OF SOLUTIONS

This general chapter provides information in support of instrumental methods for procedures that measure electrical conductivity. Pharmaceutical applications include: chemical dosing, cleaning in place, fermentation control, and liquid mixing verification, among others. Although the general chapter focuses on aqueous systems, conductivity measurements can be extended to organic fluids. The general chapter also focuses on contacting conductivity measurements and does not cover applications which may use noncontacting inductive conductivity. After an introduction, the general chapter covers the following major topics: theory of operation, operational considerations, calibration, and operation for at-line, in-line, and off-line measurement procedures.
The JP water conductivity method is different than EP and USP. Or is it?

Conductivity <2.51> When the test is performed according to the following method, the conductivity (25°C) is not more than 2.1 μS·cm⁻¹.

Transfer a suitable amount of Water for Injection to a beaker, and stir the water specimen. Adjust the temperature to 25 ± 1°C, and begin agitating the water specimen vigorously, while observing its conductivity periodically. When the change in conductivity becomes not greater than 0.1 μS·cm⁻¹ per 5 minutes, adopt the observed value as the conductivity of the water specimen.
(1) Monitoring of Conductivity by applying the Conductivity Measurements <2.51> of the JP

The Conductivity Measurements <2.51> of the JP principally require to measure the conductivity at the standard temperature (20°C). However, measurement at a temperature within a range of 15 – 30°C may also be acceptable, when the results are corrected using the equation prescribed in the Conductivity Measurements <2.51>. In this case, the recommended allowable conductivity (action level) for Purified Water and Water for Injection is as follows.

- Action Level 1.0 µS · cm⁻¹ (20°C)

Since the above allowable conductivity is established for in-line monitoring, an alternative action level may be used for the monitoring based on offline batch testing.

(2) Monitoring of Conductivity by applying the <645> Water Conductivity of the USP with some modification

Usually, it is somewhat difficult to control the temperature exactly in in-line conductivity monitoring. Therefore, the following approach can be applied for the monitoring at temperatures other than the standard temperature (20°C) of the JP. This approach is based on the Stages 1 and 2 of the three-stage approach described in "<645> WATER CONDUCTIVITY" of the USP.
Alternative JP 16 Conductivity Monitoring meets USP
INTERNATIONAL HARMONIZATION
## Harmonization: Conductivity Methods and Limits

<table>
<thead>
<tr>
<th>Parameter</th>
<th>USP</th>
<th>EP</th>
<th>JP</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductivity test required</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>2010</td>
</tr>
<tr>
<td>Eliminate chemistry tests</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Purified Water 3-stage test</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Purified Water test limits(^2)</td>
<td>1.3 (\mu)S/cm</td>
<td>5.1 (\mu)S/cm</td>
<td>1.3 (\mu)S/cm</td>
<td>?</td>
</tr>
<tr>
<td>WFI 3-stage test</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>WFI limits(^2)</td>
<td>1.3 (\mu)S/cm</td>
<td>1.3 (\mu)S/cm</td>
<td>1.3 (\mu)S/cm</td>
<td>1.3 (\mu)S/cm</td>
</tr>
<tr>
<td>Instrument requirements</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Sensor accuracy</td>
<td>±2%</td>
<td>±2%</td>
<td>yes</td>
<td></td>
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<tr>
<td>Sensor calibration method</td>
<td>not specific</td>
<td>not specific</td>
<td>yes</td>
<td></td>
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<tr>
<td>Calibration solutions</td>
<td>user selected</td>
<td>user selected</td>
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<tr>
<td>Calibration Method</td>
<td>works</td>
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<td>yes</td>
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<tr>
<td>Compensation</td>
<td>none</td>
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<td>yes</td>
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<tr>
<td>Method tested</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

1 Heavy metals and nitrates tested required for EP; aluminum test required for dialysis solutions
2 at 25°C
3 Retained ammonia and heavy metals tests
Harmonization - SWFI (E62)

- A Stage 3-Revision 4 Document (based on current USP monograph) for SWFI was written and sent by USP, as the lead pharmacopeia, to the PDG in June 2014
  - Comments received from EP (July 2014)
  - Uncertainty about changes (TOC as an alternative)
  - Comments received from JP (April 2015)
European Pharmacopoeia Commission Secretariat

RZ/PH/2014-00178L
MBU/lake

Strasbourg, 16/01/2014

Subject: E62 Sterilised Water for Injections, Stage 3 revision 3, EP Comments

LETTER FOR THE ATTENTION OF THE PDG

Dear Colleagues,

Please find attached comments from EP on the above-mentioned topic.

We look forward to receiving your feedback on this.

With kind regards,
April 18, 2013

Ms. Catherine Sheehan,
Director, Excipients,
USP

Subject: E-62 Sterile Water for Injection (CP: USP):
JP Response to USP Additional Comment on Stage 3 Proposal

JP acknowledged receipt of USP additional comment on Stage 3 proposal for E-62 Sterile Water for Injection dated January 30, 2013. We would like to thank you for your response to the JP request for the conductivity limit at NMT 15µS/cm.

The JP Expert Committee on Biological Methods reviewed the USP comment, understood the difficulty for the US manufacturers to meet the limit and agreed to change the acceptance criterion to NMT 25 µS/cm for Sterile Waters for Injection in containers with a nominal volume of 10 mL or less.
A Stage 3-Document for 〈644〉 Conductivity was written and sent by USP, as the lead pharmacopoeia, to the PDG in March 2010
  – Comments received from JP and EP (Sept 2010)
  – Good document, but too complex for a specific method
  – USP converted 〈644〉 to 〈1644〉 Theory and Practice of Electrical Conductivity Measurements of Solutions

USP created more accurate 〈644〉 Stage 4-Revision 1 and sent to the PDG in October 2013
  – Comments received from EP (Feb 2014)
  – Comments received from JP (end-2014)
  – USP created a 〈644〉 Stage 5a and sent to the PDG in August 2017 for sign off
<644> ELECTRICAL CONDUCTIVITY OF SOLUTIONS

(Harmonization DRAFT v2)

This chapter provides information to apply electrical conductivity measurements (hereafter referred to as 'conductivity') of fluid solutions, including pure fluids. This chapter does not replace the official Water Conductivity procedure which is used to assure the ionic purity of compendial waters such as Water for Injection, Purified Water, Pure Steam condensate, Sterile Water for Injection, among others. Rather, this chapter is intended for other fluid applications when conductivity is used to measure, monitor, or control chemical dispensing, chemical purity, ionic concentration, and other applications where the ionic character of the fluid needs to be known or controlled.

Applications include, but are not limited to, solutions that may be used in clean-in-place, chromatography detection, ionic solution preparations, endpoint detection, dosing, fermentation, and buffer production. In some cases, conductivity measurements can be extended to pure organic fluids such as alcohols and glycols where a weak conductivity signal exists, and the signal can be significantly increased if the organics become contaminated with water or salts.
Questions

Empowering a healthy tomorrow
Thank You

Empowering a healthy tomorrow