The use of TOC measurements for process control in Pharmaceutical Waters and CIP

Joe Gecsey
<table>
<thead>
<tr>
<th>TOC Range</th>
<th>EPA Grade Water</th>
<th>CIP Rinse Water</th>
<th>Purified Water</th>
<th>Water For Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2-8ppm</td>
<td>&lt;2ppm</td>
<td>&lt;500ppb</td>
<td>&lt;500ppb</td>
</tr>
</tbody>
</table>
**USP Requirement’s for PW and WFI**

**Incoming water must meet EPA drinking water or country regulations**

**Typical treatments:**
- Softening
- De-Ionization
- De-chlorination
- Reverse Osmosis
- Ultra-filtration

**Water For Injection**

- **Endotoxin/Microbial Reduction**
- **Packaging & Sterilization**

**Sterile WFI:**
- Irrigation
- Bacteriostatic
- Inhalation

**Purified Water**

- **Distillation**

**Purified Water:**
- Inhalation
- Drug production

**WFI – Distillation method is only method accepted by all pharmacopoeia’s**

**USP accepts double pass Reverse Osmosis method**
Compendia definition of pharmaceutical water:
“Any water intended for use in a final dosage form.”

<table>
<thead>
<tr>
<th>Bulk Water</th>
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</thead>
<tbody>
<tr>
<td>• Water for Injection (WFI)</td>
</tr>
<tr>
<td>• Purified Water (PW)</td>
</tr>
<tr>
<td>• Clean Steam (condensate)</td>
</tr>
<tr>
<td>• Water for Hemodialysis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Packaged Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sterile Purified Water</td>
</tr>
<tr>
<td>• Bacteriostatic Water for Injection</td>
</tr>
<tr>
<td>• Sterile Water for Inhalation</td>
</tr>
<tr>
<td>• Sterile Water for Injection</td>
</tr>
</tbody>
</table>

**New packaged water testing in 2014**
System Design and Typical TOC Performance

Basic system for illustration only
Global Pharmacopeias

• Importance - If you manufacture drugs for use in their country you must meet their requirements

• About 42 globally

• Most are branches of the Government

• EP, USP and ICH typically accepted internationally
Pharmacopeias - Similar but Different

Bulk Water

• USP
  • TOC levels for PW and WFI the same
  • Calibrate to manufacturer’s protocol
  • System Suitability with Sucrose and 1,4 Benzoquinone

• EP
  • TOC levels for PW and WFI the same
  • Must completely oxidize sample
  • Calibrate to manufacturer’s protocol
  • System Suitability with Sucrose and 1,4 Benzoquinone
  • Conductivity requirements for PW and WFI differ
    – WFI matches USP
Apparatus commonly used to determine TOC in water for pharmaceutical use …

• USP states “… have in common the objective of oxidizing the organic molecules in sample water to carbon dioxide…”

• EP states “… have in common the objective of completely oxidizing the organic molecules in the sample water to produce carbon dioxide…”
Requirements for PW and WFI 500ppb

- PW - 500ppb
  - Still requires periodic oxidizable substance test
- WFI – Action Limits 300ppb on-line, 400ppb off-line
• On-line TOC analyzers - Real-Time-Release
  – Calibrate with KHP (potassium hydrogen phthalate)
  – System Suitability with SDBS (Sodium Dodecylbenzene Sulfonate)
  – Minimum recovery of 450ppb

• US/European manufacturers outside Japan
  – On-line analyzer meets USP or EP requirements acceptable for use

• Laboratory TOC Analyzer – Grab Samples back to lab
  – Calibrate with KHP (potassium hydrogen phthalate)
  – System Suitability with SDBS (Sodium Dodecylbenzene Sulfonate)
  – Minimum recovery of 450ppb
JP 16 – On-line TOC Analyzers

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, phosphorous or halogen atoms in their chemical structures, is used as the source water supplied to the system.**

**EPA Grade water is acceptable source water**
### Changes to the USP 23 Monograph

<table>
<thead>
<tr>
<th>Old</th>
<th>New</th>
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<tbody>
<tr>
<td>pH</td>
<td>Deleted</td>
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<tr>
<td>Endotoxins</td>
<td>Maintained &lt;85&gt;</td>
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<tr>
<td>Calcium</td>
<td>Conductivity method &lt;645&gt;</td>
</tr>
<tr>
<td>Sulfate</td>
<td>Conductivity method &lt;645&gt;</td>
</tr>
<tr>
<td>Chloride</td>
<td>Conductivity method &lt;645&gt;</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Conductivity method &lt;645&gt;</td>
</tr>
<tr>
<td>Carbon Dioxide</td>
<td>Conductivity method &lt;645&gt;</td>
</tr>
<tr>
<td>Oxidizable Substances</td>
<td>TOC method &lt;643&gt;</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>Deleted (still part of EP)</td>
</tr>
<tr>
<td>Coliforms</td>
<td>Deleted</td>
</tr>
<tr>
<td>Microbial Count</td>
<td>Added to chapter &lt;1231&gt;</td>
</tr>
<tr>
<td>Total Solids</td>
<td>Deleted</td>
</tr>
</tbody>
</table>

- Old OS test - potassium permanganate
Existing USP <643> and <645> Test Methods

• TOC Method <643> (EP 2.2.44)
  • 500 ppb (0.5 mg/L) as determined by the limit response

• Conductivity Method <645> (EP 2.2.44)
  • Limit of 1.3 $\mu$S/cm (25°C) for Stage 1 test
  • Off-line Test 2.1 $\mu$S/cm @ 25°C
  • Limit of 4.7 $\mu$S/cm (depending on pH) for Stage 3
Definition of Carbon in Water

- TC = Total Carbon
- TIC = Total Inorganic Carbon
  - IC = Inorganic Carbon
  - Particulates
- TOC = Total Organic Carbon
  - NPOC = Non Purgable Organic Carbon
  - POC = Purgable Organic Carbon
  - Particulates
TOC is an important measure of pharmaceutical water quality using the EP, USP, JP, KP and CP methods.

“Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water system from the source water, from purification and distribution system materials, and from bio-film growing in the system, and from packaging of sterile and non-sterile waters.”
Small increases in TOC (i.e. 1-5%) can result in large increases in bacteria through reproduction and shedding of biofilm from the walls.

1. TOC “slug” increase occurs
2. Bacteria and biofilm shed to seek nutrients almost immediately.
3. Biofilm introduced into main stream.
On-line & Laboratory TOC Testing

**On-line**

+ High Purity Water
+ Continuous measurement
+ No sample handling
+ No sample contamination
+ Measure in own environment
+ True Water Levels
+ Immediate data results
+ Conductivity and Temperature for USP <645>

(-) Limited Range

**Laboratory**

+ Wide Range – All Waters
+ Multiple samples with auto-sampler
+ Independent of conductivity

(-) Need Reagents and Gas

(-) Potential Grab sample contamination

(-) Higher than True Water Levels

(-) Delayed data, infrequent results

(-) Sample tracking protocols
On-line vs. Laboratory TOC Testing
On-line TOC analyzers - Oxidation

UV emission at the origin of photo-oxidation
Low Pressure Mercury Vapor Lamps

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Relative intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>TOC Destruct</td>
</tr>
<tr>
<td>254</td>
<td>Microbial Disinfection</td>
</tr>
</tbody>
</table>
Oxidation Profiles of Sucrose and Methanol

Different Oxidation profiles for different Organics
Full Oxidation = Accuracy

TOC Oxidation Profiles

Partial oxidation

500 ppb C Sucrose

500 ppb C Methanol

Complete oxidation

High conductivity intermediates (organic acids)
On-line TOC Analysis Methods

Slow Flow – Membrane Comparison Conductivity

• CO₂ transfer through two membranes
  – Three Conductivity Sensors
  – Continuous Internal sample pumphead
  – Six minute oxidation time due to fixed flow rate
  – Internal DI water calibration loop w/pumphead
    • Transports CO₂ to conductivity sensors
    • “TOC & Conductivity autozero” cell drift correction function

  – Validation Issues
    • Plurality of Algorithms, All not calibrated, validated
    • Calibrate with acidified standards
    • No raw conductivity data from TOC cells after “autozero”

  – Meets USP, JP – yes, Follows EP - no
• Sample Stream is split
• Sample Conductivity Cell
  • Determines which preprogrammed algorithm is selected
• Two Conductivity Cells for TOC
  – No conductivity calibration
• Two Membranes
• Built in DI water system w/pump
  • Move CO2 past cond. cells
  • Sensor drift correction, “autozero TOC & conductivity” for negative TOC results
• Ion Exchange Cartridge
• DI Water Pumphead
• Sample Pump works continuously
TOC Analysis Methods

Fast Flow - Comparison Conductivity

- Partial Oxidation Multiple Conductivity Sensors
  - Continuous Fixed Flow – Water system pressure
  - Pre/Post UV conductivity measurement
  - One minute oxidation time

- TOC accuracy dependent on UV lamp intensity, flow and pressure
- Unpredictable Oxidation capabilities

Calibration is based on the incomplete oxidation of sucrose which yields organic acid intermediates and carbon dioxide.

- TOC Indicator
  - Fast Response, but sacrifice accuracy
  - Flow rate and pressure control critical
Fast Continuous Flow Comparison Method

- TOC partially oxidized by UV
- Reading from Conductivity Cell 1
- Water flowing past UV lamp
- Conductivity if TOC fully oxidized
- Reading from Conductivity Cell 2
- \((\Delta \text{conductivity}) \times \text{factors} = \text{estimated TOC}\)
Differential TOC Analysis Method

On-line TOC Analyzer – Differential Conductivity

Single Cell End Point Detection

• Two UV lamps
• Continuous short term batch
• Oxidize the organics completely to CO₂
• Meets EP & USP Conductivity, Temperature
• Validation, accuracy of single cell easy to confirm

• No fixed oxidation time

• Meets USP – yes, JP – yes, Follows EP – Yes
Single Cell End Point Detection

- Single Cell
- On-line using water system pressure
- Pump Mode for low pressure
- Grab Sample
- Bypass for continuous flow
Calculating TOC w/ Single cell Differential Method

- Organic molecules contribute ~ zero conductivity to water
- Inorganic species that contribute to initial conductivity are constant and establish baseline
- TIC - Conductivity of the un-oxidized water sample is measured
- TOC - UV light comes on. Oxidize organics to CO2 which causes conductivity to increase
- TC - Conductivity of the oxidized water sample is measured

TOC = TC - TIC
Single Cell Differential Method

TC Measurement
Dynamic end-point detection... final conductivity

TOC Measurement
$\Delta \mu$S/cm

Independent of:
- Cell Drift
- Flow rate
- Pressure
- UV Lamp Intensity
- pH
- Rouge

TIC Measurement
(Initial conductivity)

μS/cm

Time

Lamp off

Lamp on

No fixed oxidation time
USP <643> Compliance
TOC Method Requirements

Bulk Water

TOC limit of 500 ppb as determined by Standard Solution results, or Limit Response testing

Either on-line or laboratory TOC analyzers may be used as long as the analyzer meets the following criteria:

- Oxidize organic sample to CO2
  - Must completely oxidize organic sample (EP only)
- Instrument must be calibrated
- USP System Suitability test must be performed on a calibrated instrument with recovery levels of 85 -115%
- Instrument detection limit must be better than 50 ppb
• Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon.

• TOC is a required measurement of all global pharmacopeias.
• TOC analyzer must meet USP<643> and EP 2.2.44 methods

• TOC acts as a food source for microbes

• Reducing TOC reduces the possibility of microbial contamination

* USP 32 –TOC measurement is not a replacement test for endotoxin or microbiological control. While there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.
Correlation: endotoxins and TOC

Test day (3 samples/week)

TOC (ppb)  Endotoxins (EU/mL)
System Suitability Test (SST)

- System Suitability is not calibration!

- System suitability is “the process of validating whether your system (i.e. TOC analyzer) is acceptable for providing useful analytical data without any bias.”

- Confirms the analyzer is working correctly

- This is typically done by:
  1. Analyzing a material that is easy-to-oxidize (sucrose)
  2. Analyzing a material that is difficult-to-oxidize (1,4-benzoquinone)
  3. Calculating the ratio of the responses
USP <643> specifies “periodically”
EP 2.2.44 specifies “suitable intervals”

• System Suitability plan
  – Once a week for one month
  – Once a month for three months
  – Once a every quarter
  – Once every six months

• Quality system and company protocol dependent
• Re-calibration or service suggests new system suitability
• Frequency of system suitability should be determined systematically, using historical data
• Validates “Brackets” data for time period
• Instrument dependent
  – On-line require less testing
  – UV Lamp monitoring reduces frequency
Common terms in the <643> method:

- **Reagent Control Water** = $r_w$ = water used to make reagents
  Must be below 100 ppb

- **Standard Solution** = $r_s$ = 500 ppb sucrose RS

- **Standard Solution Limit Response** = $r_s - r_w$ and establishes the PW & WFI pass/fail limit (500 ppb)

- **System Suitability Solution** = $r_{ss}$ = 500 ppb 1,4-benzoquinone RS

- **System Suitability Solution Response** = $r_{ss} - r_w$

- **Response Efficiency** = $\left[ \frac{(r_{ss} - r_w)}{(r_s - r_w)} \right] \times 100 = 85-115\%$
Sterile Water Testing

- Sterile Purified Water
- Bacteriostatic Water for Injection
- Sterile Water for Inhalation
- Sterile Water for Injection

- Apparatus Limit of Detection – 100ppb

- System Suitability Test
- Reagent Water TOC Level – ≤500ppb
- Sucrose solution w/concentration of 19.0 mg/L (8 ppm)
- 1,4 Benzoquinone solution w/concentration of 12.0 mg/L (8.0 ppm)
USP <645> Conductivity

- Conductivity measures “ion-facilitated electron flow through water”
- Conductivity and resistivity are the same measurement of ionic contamination in water
  
  Ultrapure Water @25ºC  Conductivity = 0.055µS/cm  
  Resistivity = 18.18 MΩ-cm

- USP <645> introduced to reduce the number of tests for individual tests for chloride, calcium, carbon dioxide, ammonia and sulfate
- Conductivity measurement must be uncompensated
- Temperature effects conductivity measurements
- USP make allowances for different methods of testing
Three Possible Stages of Testing

Stage 1 – On-line testing (or off-line)
- Measure water temperature
- Measure the non-temperature compensated conductivity
- See chart to determine conductivity limit

Stage 2 – Laboratory testing (in Beaker)
- Equilibrate sample with air at 25° C
- Measured conductivity must be < 2.1 µS/cm

Stage 3 – Laboratory testing (same beaker as Stage 2)
- Equilibrate sample with air at 25° C
- Add saturated KCl and measure pH
- See chart to determine conductivity limit
Limits of Test Methods

TOC Method <643> (EP 2.2.44)
- 500 ppb (0.5 mg/L) as determined by the limit response

Conductivity Method <645> (EP 2.2.44)
- Stage 1 test - 1.3 μS/cm (25°C)
- Lab test – 2.1 μS/cm @ 25°C
- Lab test - 4.7 μS/cm (depending on pH) for Stage 3

Note: USP <645> and EP 2.2.44 for conductivity requirements for WFI are generally harmonized
### Stage 1 Conductivity and Temperature Limits

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Uncomp. Conductivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
</tr>
<tr>
<td>20</td>
<td>1.1</td>
</tr>
<tr>
<td>25</td>
<td>1.3</td>
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<tr>
<td>30</td>
<td>1.4</td>
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<td>35</td>
<td>1.5</td>
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<td>40</td>
<td>1.7</td>
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<tr>
<td>45</td>
<td>1.8</td>
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<tr>
<td>50</td>
<td>1.9</td>
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<td>55</td>
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<td>65</td>
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<tr>
<td>95</td>
<td>2.9</td>
</tr>
<tr>
<td>100</td>
<td>3.1</td>
</tr>
</tbody>
</table>

**USP** - WFI & PW  
**EP** - WFI  
**JP**
Stage 3: Conductivity and pH Limits
Requirements that the conductivity equipment must meet:

“…meter calibration is accomplished by replacing the conductivity cell with NIST (or equivalent) precision resistor +/-0.1%”

“The conductivity cell constant… must be known within ±2%.”

“…the instrument accuracy must be ±0.1 µS/cm.”

“… it is suggested … verification of the entire equipment be performed … compare against an external calibrated measuring device … must be with +/-20%”
Step 1 - Determining Meter Accuracy

Meter accuracy must be ± 0.1 µS/cm

Done by measuring the meter electronics response to traceable resistor(s)/decade box in the measurement range.

USP <645> Requirement: Instrument must be verified then cell constant must be confirmed.
Step 2 – Verifying the Cell Constant

Cell Constant = CC or cm/cm²
Conductance = µS
Conductivity = CC x (Cond µS) = µS/cm

- The lower the cell constant value is, the higher the water purity it can measure. (0.01, 0.1)
- Conductivity increases as a function of temperature… must be measured accurately throughout the oxidation process.
Suggested Test Procedure

In-Line System Check in UPW

Calibrated Conductivity System

Comparison check +/- 20%
1) TOC and conductivity are required measurements of pharmaceutical water quality using the USP<643>, EP 2.2.44, JP XV, KP and CP methods

2) Different methods exist for TOC analysis
   - Lab: combustion, wet oxidation
   - On-line: UV oxidation – Differential, Comparison

3) On-line analysis methodology is best suited for low level TOC found in life-science applications
4. Pharmaceutical manufacturers are moving from laboratory to on-line analysis for water release
   - FDA pursuing Process Analytical Technology (PAT) initiative

5. TOC analysis technology exists that is science and risk-based, allowing for real-time on-line release

6. On-line TOC analyzers will also provide conductivity and temperature to meet USP <645>
Thank you!!!!

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