Confidence in Compliance

Pharmaceutical Water Compliance
for Global Pharmacopeia Requirements

THORNTON
Leading Pure Water Analytics

METTLER TOLEDO
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</tr>
</tbody>
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Thornton was founded by Dr. Richard Thornton (Professor at Massachusetts Institute of Technology, MIT) in 1964 and has been part of the METTLER TOLEDO Process Analytics Division since 2001. The company's market leadership has been demonstrated by innovative analytical instruments and sensors specializing in High Purity and Ultrapure Water applications found in various industries including: Pharmaceutical, Biotechnology, Microelectronics and Power Generation.

METTLER TOLEDO Thornton personnel are active in various scientific organizations such as ASTM, ISPE, PDA, AIChE, SEMI, and USP. Extensive research has been conducted in:

- Conductivity of Ultrapure Water
- High Temperature UPW
- TOC and Ozone (O₃)
- Dissolved Oxygen and CO₂
- Calibration and Temperature Compensation

ISM® Provides Much More Than a Measurement

Intelligent Sensor Management (ISM) is a proven technology embedded in a sensor, which outputs a robust digital signal, retains unique factory and current calibration data and predicts a sensor’s need for maintenance, calibration or replacement.
1. Water Purity Standards

Purified Water (PW), Highly Purified Water (HPW), Water for Injection (WFI), and Pure Steam are used in Pharmaceutical manufacturing processes around the world. National and international authorities have established water quality standards for Purified Water and other grades of water. These key authorities include:

- United States Pharmacopeia (USP)
- European Pharmacopeia (EP)
- Japanese Pharmacopeia (JP)
- Chinese Pharmacopeia (ChP)
- Indian Pharmacopeia (IP)

2. What is USP?

The United States Pharmacopeia (USP) is a non-governmental, official public standards-setting authority for prescription and over-the-counter medicines, cosmetics, and other healthcare products manufactured or sold in the United States. USP also sets widely recognized standards for food ingredients and dietary supplements. It also sets standards for the quality, purity, strength and consistency of these products which are critical to public health. USP’s standards are recognized and used in more than 130 countries around the globe. These standards have helped to ensure public health throughout the world for close to 200 years.

2.1 Conductivity and Total Organic Carbon (TOC) for Monitoring the Purity of Water

Conductivity and Total Organic Carbon (TOC) are measurements for ionic and organic impurity control in bulk Purified Water, Water for Injection and the condensate of Pure Steam. Chapters 645 Water Conductivity and 643 Total Organic Carbon of the United States Pharmacopoeia provided the first test methods for equipment verification, on-line process control and release of water to production. USP specifications do not limit or prevent alternative technologies from being used, but provide guidance on how to qualify these analytical systems, interpret instrument results and set standards for the measuring instrumentation used for TOC and conductivity such as a System Suitability Test (SST), limit of detection, instrument resolution and calibration requirements for sensor and transmitter or measurement electronics.
3. Goals of USP <645>

1. Ensure integrity of existing water quality
2. Replace outdated wet chemical tests
3. Quantify test results
4. Encourage on-line testing
5. Mitigate the amount of testing required
6. Improve testing reliability

3.1 USP <645> Conductivity

Bulk waters for pharmaceutical purposes include Water for Injection, Highly Purified Water, Purified Water and Pure Steam. Most global pharmacopeias have stated requirements for producing these waters. In the United States, the regulations for conductivity are addressed by the U.S. Pharmacopeia in test chapter <645> which is harmonized with other global pharmacopeias. Conductivity testing is a requirement for USP Purified Water, Water for Injection and the condensate of Pure Steam. USP <645> is a 3-stage test method which entails either on-line or off-line testing. On-line conductivity testing is covered by Stage 1, while Stage 2 and 3 represent off-line testing. In December 2008, USP <645> was amended to encourage the use of on-line testing:

“On-line conductivity testing provides real-time measurements and opportunities for real-time process control, decision and intervention. Precaution should be taken while collecting water samples for off-line conductivity measurements. The sample may be affected by the sampling method, the sampling container and environmental factors such as ambient carbon dioxide concentration and organic vapors.”

3.1.1 Advantages of On-line Testing

There are several advantages for performing on-line testing. One key advantage is that with on-line testing, errors associated with collecting, handling and transport of the sample are mitigated or eliminated. In addition, as water is produced and consumed continuously, on-line testing enables the collection of real-time data which can be recorded and analyzed providing real-time process information and a complete water history. On-line testing provides a simple, cost-effective measurement alternative to off-line testing.

Simplified Compliance
ISM simplifies regulatory compliance by storing sensor calibration data internally and reducing written record keeping.
3.2 Temperature and USP <645>

Temperature is a key parameter for observing changes in water quality as it can have a significant impact on conductivity measurements of water samples. USP <645> describes the importance of temperature this way:

“Because temperature has a substantial impact on conductivity readings of water samples at high and low temperatures, many instruments automatically correct the actual reading to display the value that would theoretically be observed at 25°C. This is typically done through the use of a temperature sensor embedded in the conductivity sensor and an algorithm in the instrument’s circuitry. This temperature compensation algorithm may not be accurate. Conductivity values in this method are non-temperature-compensated measurements.”

In other words, because temperature compensation algorithms between manufacturers lack reproducibility, USP <645> requires conductivity measurements that are non-temperature-compensated. METTLER TOLEDO Thornton instruments enable reporting uncompensated and compensated measurements using the same transmitter and sensors.

3.3 <645> Conductivity Procedure

3.3.1 Stage 1

Stage 1 is intended for on-line measurement.

On-line temperature and non-temperature-compensated conductivity are measured. The measured temperature value is rounded down to the next lowest 5°C interval and the adjusted temperature reading is located on the table below. If the measured conductivity is not greater than the limit in this table, the water meets the requirements for <645>.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Maximum Conductivity (µS/cm)</th>
<th>Temperature (°C)</th>
<th>Maximum Conductivity (µS/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.6</td>
<td>55</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>60</td>
<td>2.2</td>
</tr>
<tr>
<td>10</td>
<td>0.9</td>
<td>65</td>
<td>2.4</td>
</tr>
<tr>
<td>15</td>
<td>1.0</td>
<td>70</td>
<td>2.5</td>
</tr>
<tr>
<td>20</td>
<td>1.1</td>
<td>75</td>
<td>2.7</td>
</tr>
<tr>
<td>25</td>
<td>1.3</td>
<td>80</td>
<td>2.7</td>
</tr>
<tr>
<td>30</td>
<td>1.4</td>
<td>85</td>
<td>2.7</td>
</tr>
<tr>
<td>35</td>
<td>1.5</td>
<td>90</td>
<td>2.7</td>
</tr>
<tr>
<td>40</td>
<td>1.7</td>
<td>95</td>
<td>2.9</td>
</tr>
<tr>
<td>45</td>
<td>1.8</td>
<td>100</td>
<td>3.1</td>
</tr>
<tr>
<td>50</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.3.2 Stage 2 & 3

Off-line tests have different requirements and results can be more difficult to achieve. In both Stage 2 and 3, the sample is stirred (to equilibrate the water sample with atmospheric CO₂) and the temperature is adjusted to 25° ± 1°C. If the conductivity is less than 2.1 μS/cm, the water meets the requirements of <645>.

However, if the water sample is greater than 2.1 μS/cm, the user proceeds to Stage 3. In Stage 3, the sample temperature is maintained at 25°C ± 1°C. A saturated potassium chloride solution is added to the water sample and pH is determined to the nearest 0.1 pH unit. If the conductivity reading from Stage 2 is not greater than the conductivity referenced for a given pH value (see Table 2 in USP <645>), it meets the requirements of <645>. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0 - 7.0, the water does not meet the requirements of <645> for conductivity.

3.4 Summary of Calibration Requirements for USP <645>

The conductivity of water must be measured accurately using calibrated instrumentation. USP <645> has calibration requirements for both the transmitter and measurement electronics as well as the sensor. The requirements for transmitters or measurement electronics (for digital sensors) include:

- Temperature measurement circuit verified.
- Reports uncompensated conductivity or resistivity.
- Display resolution of 0.1 μS/cm. 1.0 μS/cm resolution is not acceptable.
- Verify performance to ± 0.1 μS/cm by replacing sensor with traceable precision (0.1%) resistor. For example: 50 kΩ resistor with 0.1 cm⁻¹ cell constant should display 2.0 ± 0.1 μS/cm.

### Transmitter Requirements and METTLER TOLEDO Thornton Transmitters

<table>
<thead>
<tr>
<th>USP Specification</th>
<th>M800 (ISM®)</th>
<th>M300 (ISM)</th>
<th>M300 (Analog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistors accurate to 0.1% of stated accuracy, traceable to NIST or equivalent national authority</td>
<td>0.05% - 0.1% NIST traceable</td>
<td>0.05% - 0.1% NIST traceable</td>
<td>0.05% - 0.1% NIST traceable</td>
</tr>
<tr>
<td>Instrument accuracy without sensor at 1.3 μS/cm is ± 0.1 μS/cm</td>
<td>±0.004 μS/cm (±0.3% of reading)</td>
<td>±0.004 μS/cm (±0.3% of reading)</td>
<td>±0.004 μS/cm (±0.3% of reading)</td>
</tr>
<tr>
<td>Instrument display resolution to 0.1 μS/cm</td>
<td>0.001 μS/cm</td>
<td>0.001 μS/cm</td>
<td>0.001 μS/cm</td>
</tr>
<tr>
<td>Must report non-temperature-compensated conductivity or resistivity</td>
<td>Reports non-temperature-compensated and temperature-compensated conductivity or resistivity</td>
<td>Reports non-temperature-compensated and temperature-compensated conductivity or resistivity</td>
<td>Reports non-temperature-compensated and temperature-compensated conductivity or resistivity</td>
</tr>
</tbody>
</table>
The USP <645> calibration requirements for conductivity sensors include:

- Temperature accurate to ± 2°C.
- Cell constant accurate and known to ± 2%.
  - Calibrate sensor in a solution with stated conductivity (from NIST, chemical supplier, etc.).
  - Calibrate sensor in a solution prepared to a specific conductivity (ASTM D1125 standard or ultrapure water).
  - Calibrate sensor vs. another calibrated sensor usually from the same manufacturer.

3.5 Recommended Process for Calibration

In general, a complete measuring system consists of: the measuring electronics or transmitter, which typically contain the measurement circuit, the sensor and the cable linking the sensor and transmitter. The following parameters must be fully calibrated to produce a calibrated system:

1. The measuring electronics or temperature circuit
2. The measuring electronics’ resistance circuit
3. The sensor temperature element
4. The sensor cell constant

<table>
<thead>
<tr>
<th>Sensor Requirements and METTLER TOLEDO Thornton Sensors</th>
<th>UniCond® Sensors</th>
<th>Analog Sensors</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Specification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell constant accuracy: ± 2% using reference solution (e.g. ASTM D1125 or other reference solution)</td>
<td>Cell constant accurate ± 1%</td>
<td>Calibration traceable to ASTM D1125, D5391, and Ultrapure Water</td>
</tr>
<tr>
<td>Temperature accuracy: ± 2°C</td>
<td>± 0.1°C at 25°C</td>
<td>Temperature traceable to NIST</td>
</tr>
</tbody>
</table>

3.5.1 Transmitter or Measurement Electronics Calibration

When transmitters or measuring electronics are calibrated, it is important to verify and calibrate all range resistors and the internal circuitry. This is traditionally done through the use of a decade box or a manufacturer’s calibration device. In these devices, traceable resistors are used to simulate temperature and conductivity. Measured temperature and conductivity are then compared to the traceable temperature and resistivity. Adjustments are then made as needed to calibrate the electronic circuitry.
3.5.2 Sensor Calibration

Cell Constant: Although a sensor cell constant may have a nominal value of, for example, 0.1 cm\(^{-1}\), the precise cell constant is typically calibrated individually to achieve higher accuracy. This is done using a known solution in comparison with another calibrated measuring system. Factory calibrations of cell constant are certified and traceable to an ASTM standard while temperature is traceable to NIST.

**Thornton 0.1 cm\(^{-1}\) Conductivity Sensor**

Conceptual Drawing of Cell Constant

\[
\text{Conductivity Cell Constant} = \frac{\text{Length}}{\text{Area}} = \frac{0.1 \text{ cm}}{1 \text{ cm}^2} = 0.1 \text{ cm}^{-1}
\]

Length – distance between electrodes
Area – effective cross-sectional area of fluid between electrodes

3.5.3 Typical Methods Used to Verify/Calibrate Sensor Cell Constant

Calibrating the cell constant of a sensor can be achieved using several methods.

1. Verification or calibration of the sensor vs. another calibrated sensor.
2. Verification or calibration of the sensor in a solution with a known conductivity. Conductivity solutions for this purpose may be purchased or they may be prepared to a specific conductivity value using ASTM standard methods or Ultrapure Water.

When calibrating the sensor cell constant, a calibrated transmitter and a similar cable length should be used.

**Easy Sensor Handling**

ISM sensors are pre-calibrated, providing error-free operation with Plug and Measure simplicity.
3.5.4 Typical Method Used to Verify/Calibrate Sensor Temperature (RTD)

Calibrating temperature typically involves comparing the measured temperature with a reference temperature. When verifying and calibrating temperature, a calibrated transmitter or measurement electronics and a similar length of cable should be used and the temperature reference system should be incorporated into the same fluid and container.

3.5.5 Calibration of Cell Constant Using Digital Conductivity Sensors

The UniCond® Conductivity/Resistivity Sensor advancement integrates the measuring circuit and the physical sensor into a single unit. Sensor and measuring circuit are inseparable and they are factory calibrated as a system at the same time, resulting in a single limit of error, the same as a traditional analog sensor by itself. The digital transmitter in this case is not involved in the measurement circuit and thus introduces zero error.

Compliance with USP <645> requires calibration of both the sensor cell constant as well as the measurement circuit. The measurement circuit is traceable to NIST and the cell constant traceable to ASTM. Measuring circuit of UniCond sensors are calibrated prior to assembly.

In the case of the UniCond Sensor, the measurement circuit is incorporated within the sensor itself and not the transmitter, and the UniCond Calibration Module is uniquely suited to enable calibration of the measurement circuit while installed in the process.

3.5.6 Frequency of Calibration

In order to comply with USP test guidelines and good metrology practices, calibration must be done periodically. Most pharmacopeias, including the USP, do not specify a frequency for calibration; this is left to the recommendations of individual manufacturers. Industry norms typically suggest that calibration be performed annually.
4. **USP <643> Total Organic Carbon**

Total Organic Carbon is a measure of organic impurities present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from source water, from purification and distribution system materials and from biofilm growing in the system.

A number of acceptable methods exist for analyzing TOC. USP Chapter <643> does not endorse or limit one method over another, but it provides guidance on how to qualify these technologies and how to interpret their results for use as a limit test. All methods must discriminate between inorganic carbon, present in water from sources such as dissolved CO$_2$ and bicarbonate and the CO$_2$ generated from the oxidation of organic molecules.

USP <643> uses the following criteria to establish acceptance of TOC instrumentation:

1. Must have Limit of Detection of <0.05 mg carbon/L or 50 ppb of TOC
2. Must be calibrated according to manufacturer recommendations
3. Must distinguish inorganic carbon, i.e., CO$_2$, HCO$_3^-$ from the CO$_2$ generated from the oxidation of organic molecules
4. Must pass System Suitability Test (SST) periodically

4.1 **System Suitability Test (SST)**

Because organic carbon appears in various forms in nature and in water treatment processes, a wide variety of oxidation states and chemical forms are found in sample waters. The purpose of the System Suitability Test is to challenge the TOC instrument by verifying that it responds equally to two types of organic chemicals that challenge its measurement capability. USP <643> specifies these chemicals as Sucrose and 1, 4-Benzquinone. Due to their different chemical structure, Sucrose and 1, 4-Benzquinone challenge the bond-breaking and oxidation capability of the TOC measurement technology. USP <643> requires that SST be performed periodically on a calibrated instrument.

4.2 **The SST Procedure**

1. Measure TOC of water used to prepare these solutions, $R_w$  
   
   ($R_w$ should not exceed 0.1 mg C/L (100 ppb))
2. Measure TOC of 0.50 mg C/L (500 ppb C as sucrose), $R_s$
3. Measure TOC of 0.50 mg C/L (500 ppb C as p-benzoquinone), $R_{ss}$
4. Response should be between 85 and 115%

\[
\text{Response} = 100 \times \frac{R_{ss} - R_w}{R_s - R_w}
\]
5. EP, JP, ChP, IP and other Pharmacopeias’ Requirements

The purpose of any country’s pharmacopeia is to provide a legal compendium* of enforceable standards for product identity, purity and strength, i.e., its quality. In order to market products in a specific country, that country’s compendia is required to be met. There are over 40 compendia worldwide, with many compendia enforceable by multiple countries. As a result, if you are a producer of products that are intended to be sold in multiple countries, you will need to meet the compendia of multiple countries.

For the past two decades, the USP has been working closely with the European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) as a part of the Pharmacopeia Discussion Group (PDG). This group pursues a path to “Harmonization” of monographs and general chapters. The definition of Harmonization is “a pharmacopeia general chapter or other pharmacopeia document is harmonized when a pharmaceutical substance or product tested by the document’s harmonized procedure yields the same results, and the same accept/reject decision is reached.” The purpose of Harmonization is to develop consistent specifications, tests/procedures and acceptance criteria for pharmaceutical substances and drugs. The benefit to the pharmaceutical industry is the creation of one consistent set of tests, not differing tests, such that one set of tests satisfy the identity, purity and strength requirements of each country, thereby reducing and simplifying non-value added testing.

Harmonization is an ongoing process and its application to pharmaceutical waters has been underway since 2000. The primary efforts to harmonize pharmaceutical waters have been towards Purified Water and Water for Injection, the most common forms of water used in pharmaceutical manufacturing. Because these waters are produced and used at every pharmaceutical manufacturer, there is great industry incentive to support a harmonized set of tests for Purified Water and Water for Injection. Since 1996, the USP has led the effort to replace former wet chemical tests with conductivity and TOC limit tests along with proper instrumentation specifications. In 2000, the EP began to adopt similar conductivity and TOC tests, although not identical to USP, and in the late 2000s, the JP also began a similar adoption of these analytical tests.

The specific details of the individual pharmacopeias vary, but the “Big 3” pharmacopeias have gone from no Harmonization in the 1990s to a very high degree of Harmonization. For example, the chemical (conductivity and TOC) and microbial purity tests for WFI are harmonized completely, although the permissible methods of production vary. On the other hand, the permissible methods of production for Purified Water are consistent across the three regions, but the conductivity limits for EP are higher than the conductivity limits in USP and JP.
As the world becomes smaller and industrial manufacturing becomes more global, other pharmacopeias such as the Indian (IP) and Chinese (ChP), to name only two, are becoming more relevant. While these country’s pharmacopeias are not official members of PDG, they do follow where the other pharmacopeia are going. These and other pharmacopeia are adopting the same type of chemical purity standards that have been and are being led by the USP. While some chemical tests do remain, conductivity and TOC are the primary indicators of chemical purity and water system process control.

*The tests or specifications described above are subject to change. Use the relevant and current pharmacopeia to determine current specifications.

Bulk Purified Water and Water for Injection

<table>
<thead>
<tr>
<th>Attribute</th>
<th>USP</th>
<th>EP</th>
<th>JP</th>
<th>ChP water or Purified Water</th>
<th>IP water or Purified Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source Water for PW and WFI</td>
<td>US, EU, Japan, WHO drinking water</td>
<td>Human consumption</td>
<td>JP water specification</td>
<td>Potable water or Purified Water</td>
<td>Potable water or Purified Water</td>
</tr>
<tr>
<td><strong>PURIFIED WATER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production Method</td>
<td>Suitable process</td>
<td>Suitable process</td>
<td>Distillation, ion-exchange, UF, or combination</td>
<td>Distillation, ion-exchange, or suitable process</td>
<td>Distillation, ion-exchange, or suitable process</td>
</tr>
<tr>
<td>Total Aerobic (cfu/mL)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Conductivity (μS/cm at 25°C)</td>
<td>1.3 (3 stage)</td>
<td>5.1 (1 stage)</td>
<td>1.3 on-line or 2.1 off-line</td>
<td>5.1 (1 stage)</td>
<td>1.3 (3 stage)</td>
</tr>
<tr>
<td>TOC (mg/L)</td>
<td>0.5</td>
<td>0.5 (optional)</td>
<td>0.5 (0.3 for control)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Nitrate (ppm)</td>
<td>0.2</td>
<td></td>
<td>0.2 (optional)</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Acidity/Alkalinity</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonium (ppm)</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxidizable Substances</td>
<td>Required</td>
<td></td>
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</tr>
</tbody>
</table>

**WATER FOR INJECTION**

<table>
<thead>
<tr>
<th>Production Method</th>
<th>Distillation or suitable process</th>
<th>Distillation</th>
<th>Distillation or RO with UF, from Purified Water</th>
<th>Distillation</th>
<th>Distillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Aerobic (cfu/100 mL)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Conductivity (μS/cm at 25°C)</td>
<td>1.3 (3 stage)</td>
<td>1.3 (3 stage)</td>
<td>1.3 on-line or 2.1 off-line</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>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Bacterial Endotoxins (EU/mL)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Nitrate (ppm)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2 (optional)</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acidity/Alkalinity</td>
<td>Required</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonium (ppm)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Shaded boxes – no test required
Pharmaceutical Calibration and Test Requirements for Conductivity

**CONDUCTIVITY ELECTRONICS (RESISTANCE MEASUREMENT)**
- Calibration required, frequency not specified, determined by owner, annual calibration accepted.
- Temperature measurement circuit to be verified.
- Instrument reports uncompensated conductivity or resistivity.
- Display resolution of 0.1 μS/cm minimum. 1.0 μS/cm resolution is unacceptable.
- Verify performance to ±0.1 μS/cm by replacing sensor with traceable precision (0.1%) resistor. For example: 50 kΩ resistor with 0.1 cm⁻¹ cell constant should display 2.0 ± 0.1 μS/cm.

**CONDUCTIVITY SENSOR**
- Cell constant known to ± 2%.
  - Calibrate sensor in a solution with a stated conductivity (from NIST or certified solution).
  - Calibrate sensor in a solution prepared to a specific conductivity (ASTM D1125 standard or ultrapure water).
  - Calibrate sensor vs. another calibrated traceable sensor – performed in-line or in-lab or return to manufacturer.
- Temperature accurate to ± 2 °C.

**Pharmaceutical Calibration and Requirements for TOC**

**TOC REQUIREMENTS**
- Instrument must have a Limit of Detection of 0.050 mg C/L (50 ppb TOC).
- Calibrate according to manufacturer’s recommendations.
- Must distinguish inorganic carbon, i.e., CO₂, HCO₃⁻ from organic carbon.
- Must meet System Suitability Test (SST) periodically.

**SYSTEM SUITABILITY TESTING (SST)**
- Measure TOC of water used to prepare these solutions, R_w. Not to exceed 100 ppb.
- Measure TOC of solution prepared to concentration of 0.50 mg carbon/L (as sucrose), R_s.
- Measure TOC of solution prepared to concentration 0.50 mg carbon/L (as p-benzoquinone), R_SS.
- The accepted frequency for testing is upon UV lamp change.
- Response shall be between 85 and 115%.

\[
\text{Response} = 100 \times \left( \frac{R_{SS} - R_w}{R_s - R_w} \right)
\]
6. METTLER TOLEDO Thornton Contributions to Standards Development

When conductivity and TOC were proposed to replace wet chemical test methods in 1991, METTLER TOLEDO Thornton was already in the forefront of industry leadership and standards development. ASTM methods for conductivity were premised on work done by Dr. Thornton, our founder, in 1989 and prior years. The company’s technical leadership continued with papers in 1994 by Drs. Morash and Bevilacqua, and in 2004 by Drs. Licht, Light, Bevilacqua and Morash published in the peer-reviewed science journal, Electrochemical and Solid-State Letters.

These technical articles, in conjunction with Thornton’s leadership in conductivity/resistivity measurement systems for the microelectronics industry, paved the way for contributions to the USP. These papers were focused on conductivity measurements for the microelectronics industry’s demand for ultra-high purity waters. This industry’s need for large volumes of verifiable ion-free water was well-established, as was Thornton’s leadership in the science of ultrapure water chemistry. Subsequently, the review of Thornton’s scientific literature led the pharmaceutical industry and USP to seek analytical instrumentation and water purification expertise from Thornton.

Compliance comes easy with METTLER TOLEDO

ISM helps to ensure production process control for consistent desired product quality and yield.

M800
- Multichannel (2 or 4) transmitter with multi-parameter measurement flexibility
- Intelligent Sensor Management (ISM)
- Plug and Measure simplicity
- iMonitor – predictive maintenance
- Dynamic Lifetime Indicator
- Trending graphics for all sensors
- Assured compliance with pharmacopeia regulations

Simple menu operation with unparalleled performance and accuracy.

M300
- Multichannel (2) transmitter with multi-parameter measurement flexibility
- Intelligent Sensor Management (ISM)
- Plug and Measure simplicity
- Measurements are available within seconds of connection
- Meets all pharmacopeias’ requirements for calibration

Quick and easy installation thanks to Plug and Measure sensor capabilities.
In 1994, our effort began with the conversion of chemical tests into a relevant conductivity limit test, i.e., if you passed the conductivity test, you would necessarily pass all of the six existing chemical tests. The adoption of this conductivity test has since replaced these six chemical tests. Likewise, with the technical challenges posed by temperature compensation, Thornton developed a methodology to create a set of on-line, temperature-dependent, conductivity limits, thereby allowing one to make conductivity measurements at the process temperature without temperature compensation.

In 2000, the USP created the Pharmaceutical Waters Expert Committee, a newly-formed expert committee with the responsibility of developing and maintaining the legal definitions for water monographs and its related test chapters. The USP elected a current METTLER TOLEDO Thornton staff member as its Chair for a 5-year term, and then was re-elected him for another 5 years from 2005-2010. This expert committee, as a stand-alone group, is now concluded, but the “water oversight” responsibility now lies with the same METTLER TOLEDO Thornton expertise on the USP Chemical Analysis Expert Committee.

The work done by METTLER TOLEDO Thornton and the leadership of the USP led to the expansion of the conductivity and TOC tests of the USP. These tests, known as <643> Total Organic Carbon and <645> Water Conductivity, led to the adoption of these same analytical limit tests in the EP, JP and other pharmacopeias around the world. Today, these specific tests done for global pharmacopeias are premised on the pioneering work of Dr. Thornton and his successors over the last 50+ years.

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**Thornton’s Intelligent Sensor Management (ISM®)**

**5000TOCi with ISM**
- Complete process control and precise data trending
- Plug and Measure functionality
- Instant notification of excursion
- Simplified record keeping for SST and CAL
- Trouble-free maintenance
- Robust, reliable design virtually free from moving parts
- Compliant with all pharmacopeias

Delivering the power of an analyzer with the convenience of a sensor.

**UniCond® with ISM**
- Conductivity Factory Calibration data stored internally in sensor
- Plug and Measure functionality
- Integral high-performance measuring circuit
- Robust digital output signal
- Complete calibration for pharmaceutical compliance

Calibration tracked by iMonitor (M800) to ensure compliance.

**Ozone with ISM**
- Rapid, accurate response
- Easy maintenance with drop-in membrane
- Plug and Measure functionality
- Positive zero detection
- Assured compliance with “no added substance” rule

Confidently monitor complete sanitization and confirm ozone destruction.
Continuous, real-time, in-line measurements
for batch-to-batch consistency and quality for
the pharmaceutical industry

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