Water Technologies & Solutions
application note

Sievers* Lean Lab

Simultaneous Stage 1 Conductivity and TOC Lab Testing of Pharmaceutical Water

challenge

The United States Pharmacopeia and National Formulary (USP-NF) has been the official compendia under the United States Food and Drug Administration (FDA) since the Pure Food and Drug Act of 1906.[1]

Within the USP-NF regulations, there are four tests mandated of water for pharmaceutical purposes including Ultra-Pure Water (UPW), Water for Injection (WFI), Water for Hemodialysis, and Pure Steam. These four tests include conductivity, Total Organic Carbon (TOC), endotoxin, and bioburden (**Figure 1**). These tests are mandated to ensure product integrity, efficacy, and patient safety. Failure to comply with these regulations can have consequences ranging from product recall to endangering patient safety. As such, there is a high emphasis and scrutiny on the deployment of the analytic methods prescribed for each of these regulations.

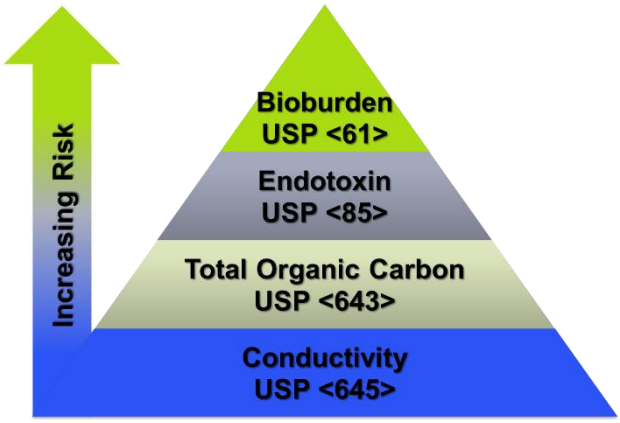

Figure 1: FDA/USP required testing for pharmaceutical water

The USP regulations listed in **Figure 1** each have an acceptance criterion limit specifically defined within the regulation. Mere compliance with the regulation can be achieved with a limit test; however, regulators and industry groups are emphasizing the importance of quantitative testing for greater process understanding and actionable data below acceptance criteria limits.

solution

Sievers M9 TOC Analyzers are designed to meet and exceed the quantitative analytical requirements per USP <1225>.[2] This allows the M9 Analyzer to be used beyond basic limit testing for TOC to include process understanding and actionable data below the acceptance criterion limit for USP <643>.

In addition to quantitative testing of TOC for compliance with USP <643>, the M9 Analyzer has an option for simultaneous Stage 1 conductivity testing for compliance with USP <645>. Although conductivity is a relatively fundamental measurement, the theory behind it can be quite technical and needs to be addressed. For a full technical explanation on conductivity and how the M9 Analyzer complies with USP <645>, please see our white paper, "Electrical Conductivity, Temperature Dependence, & Sievers M9 Analyzer".[3]

technology

To summarize the aforementioned white paper, electrical conductance, **G**, is the inverse of electrical resistance, **R**. Electrical resistance is defined by Ohm's Law as:

$$R = \frac{V}{I}[=]\ \Omega$$

Where **R** is the resistance, **V** is the applied voltage, and **I** is the measured current. While resistance is measured in Ohms (Ω), conductance, **G**, is measured in Siemens (S).

$$G = \frac{1}{R} = \frac{I}{V}[=]S$$

To measure conductivity, a probe or flow through cell is used to measure the current across a known voltage potential. Conductivity probes or cells employ two or more electrodes of known dimension across a known voltage potential. The current is directly measured and the conductance is then calculated.

Conductivity is the normalized conductance value based on the cell constant which accounts for the cell dimensions.

The principles for measuring conductivity for a manual meter and probe are the same for a conductivity flow through cell, as used in the M9 Analyzer (**Figure 2**). Where previously a time-consuming manual meter and probe were used for conductivity testing, now the exact same technology can be automated to make compliance testing fast, efficient, and reliable using the M9 Analyzer conductivity cell.

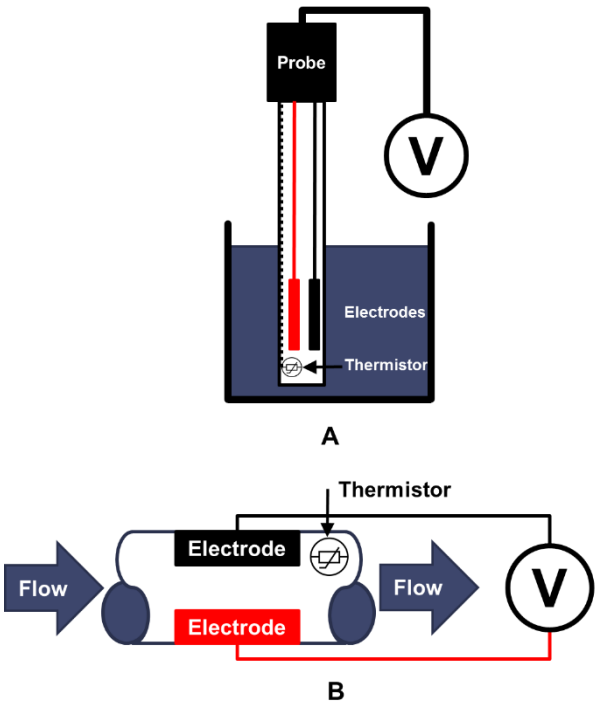

Figure 2: (A) Manual meter and probe, (B) M9 Analyzer conductivity cell

USP <645> and the M9 Analyzer

The performance of the M9 Analyzer conductivity cell meets and exceeds all instrument specifications and operating parameters set forth in USP <645>. The M9 Analyzer measures Stage 1 conductivity by simultaneously measuring non-temperature compensated sample conductivity and temperature. The M9 Analyzer also provides the necessary acceptance criteria tables for USP, EP, China Pharmacopeia (CP), and India Pharmacopeia (IP). Additional information regarding the accuracy, precision, range, and linearity for the M9 Analyzer conductivity cell can be found in **Table 1** and **Figure 3**.[4]

Table 1: M9 Analyzer conductivity specifications

Parameter	Specification
Accuracy	+/- 0.005 µS/cm or 1% whichever is greater
Precision	<0.25% RSD
Range	0.01 - 2000 µS/cm

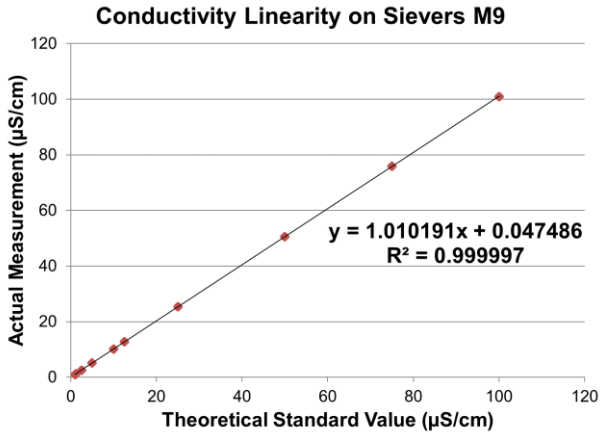

Figure 3: M9 Analyzer conductivity linearity

Additionally, USP <645> specifies three stages for conductivity testing: Stage 1, Stage 2, and Stage 3. Stage 1 is the only testing that can be performed either online or offline in the lab. Stage 1 is also the simplest method, but contains the strictest pass/fail criteria.

"Stage 1 is intended for online measurements or may be performed offline in a suitable container." - USP <645>

For offline Stage 1 conductivity testing, the user need only measure the sample temperature and the raw conductivity in a suitable container. The pass/fail criteria are provided with a temperature indexed table within USP <645>. If the sample does not pass Stage 1 conductivity acceptance criteria, additional tests must be performed (Stages 2 and 3) to determine whether the excessive conductivity is due to intrinsic factors, such as atmospheric CO_2, or extraneous ions.

Stage 2 conductivity testing is much more prescriptive in the procedural steps that must be taken. The sample must be vigorously agitated while maintaining a temperature of 25° +/- 1° C until the change in conductivity is less than 0.1 µS/cm per 5 min. Once the conductivity reading is stable, the value must not be greater than 2.1 µS/cm to pass Stage 2. Manual meter and probe Stage 2 conductivity testing can take up to 30 minutes per sample.

For pharmaceutical manufacturers, the most desirable state for compliance with USP <645> is Stage 1 conductivity testing. It is the simplest to execute, requiring the least time per sample. Automating the testing for USP <645> offers significant time savings as well as increased data integrity and security.

suitable containers

Beyond the performance of the conductivity cell of the M9 Analyzer, suitable containers for conductivity testing also need to be addressed. USP <645> specifically mentions the phrase "suitable container" in the regulation but fails to specify what qualifies as a suitable container.[5]

Performing simultaneous Stage 1 conductivity and TOC from the same vessel requires that the vessel not contribute in any significant way to either conductivity or TOC. Using a Dual Use Conductivity and TOC (DUCT) vial, the M9 Analyzer enables the end user to automate the testing for compliance with USP <643> and <645>.[6] DUCT vials are a proprietary coated glass vial with a specialty cap that has been proven to not only be suitable for conductivity and TOC testing, but superior to many of the established vessels used today.[7]

result

The FDA and USP have established TOC and conductivity as two of the four critical attributes for water quality assurance for pharmaceutical use. Manual laboratory testing of both parameters however, can take hours of analyst time. Manual meter and probe Stage 2 conductivity testing can take up to 30 minutes per sample and does not include TOC. This time-consuming process includes testing samples, recording data, and waiting on review and approval. By automating simultaneous Stage 1 conductivity and TOC testing, there is no additional time required for the conductivity measurement.

A Global Biotechnology Company located in the US was motivated to find a testing platform for both TOC and conductivity that would gain efficiency, lean out processes, and enable results to be exported to the laboratory information management system (LIMS).[8]

The simultaneous measurement of Stage 1 conductivity and TOC from a single DUCT vial with an M9 Analyzer enabled this Global Biotechnology Company to have a 5-year return on investment (ROI) of 400%, a payback period of seven months, and a 5-year net present value of approximately $400,000 for the project. The most striking aspect of the ROI is, despite the consumable cost increase due to the integration of the DUCT vials, the reduction in the time per sample and number of samples which resulted in significant overall savings to the company.[8]

This is an excellent example of how implementation of combined TOC and USP Stage 1 conductivity testing using the M9 Lab TOC Analyzer can save companies time and money while simultaneously building quality into their processes. This approach also allows organizations to redirect resources to other operational excellence and lean initiatives.[8]

This application note addressed deployment of the M9 Analyzer with Stage 1 conductivity solely in an offline, laboratory setting. However, the laboratory is not the only option. In alignment with the FDA Process Analytical Technology (PAT) Guidance, the M9 Analyzer with Stage 1 conductivity is also available in a portable configuration for at-line testing or in an online configuration for the ultimate in efficiency.

SUEZ offers complete solutions, service, and support for your water quality and cleaning application needs from instruments, standards, and vials to service, maintenance, and technical support. Thank you for choosing Sievers products as your solution.

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