

Perform Conductivity Measurements In Compliance with USP <645>

“Water is the most widely used substance, raw material, or ingredient in the production, processing and formulation of compendial articles.” Chapter 1231 of the United States Pharmacopeia (USP) begins with these words in the article “Water for pharmaceutical purposes.”

In 1996, the USP developed a new method, proposed by the Water Quality Committee of the US PhRMA, in order to control and measure the quality of the water used for all pharmaceutical products wishing to enter the US market, regardless of where they are produced. This method, USP <645>, defines the suitability of Purified Water (PW) and Water for Injection (WFI) samples through conductivity readings. The raw materials used during the manufacture of pharmaceutical products have a strong impact on the quality of the final product. For this and safety reasons, all products, testing labs or quality control for pharmaceutical industry must comply with the USP requirements.

This article provides a detailed description of the USP <645> requirements, and a guidance on the instrumentation specifications and usage, along with tips and tricks on how to meet with the norm's specifications in a clear, easy and defined way.

Contents

1.	Instrument specifications and operating parameters	2
2.	Procedure	5
3.	Challenges and how to overcome them	7
4.	Conclusion	8
5.	References	8

1. Instrument specifications and operating parameters

USP <645> outlines the requirements of the conductivity measuring system, including the conductivity meter and sensor. Those requirements have implications on the calibration and verification standards used. Several considerations are discussed in this section.

a) Conductivity meter calibration

In order to give a predicted instrument conductivity response, the conductivity meter needs to be calibrated. This process describes the calibration of sensor inputs on the meter by replacing the sensor with a service tool. This tool is typically a set of certified resistors or a decade box.

The meter calibration is achieved by using NIST-traceable resistors (or equivalent), which have an accuracy of $\pm 0.1\%$ of the stated value. This accuracy level can also be achieved through adjustable resistance devices, like a Wheatstone bridge for instance.

USP requires that the accuracy of the resistors used for meter calibration be within $\pm 0.1\%$. The resistors used by METTLER TOLEDO (MT) service technicians are NIST traceable, and the real value of the resistor is known to a precision of $\pm 0.001\%$. When a meter calibration is performed, the true resistor value (not the nominal value) is used. The true value of the certified resistor may differ from the nominal value by up to 0.3%. Note that the uncertainty value is the critical component to USP compliance here, not the difference between nominal and real value.

In addition, USP requires a minimum resolution of 0.1 $\mu\text{S}/\text{cm}$ and an instrument accuracy of $\pm 0.1 \mu\text{S}/\text{cm}$ at 1.3 $\mu\text{S}/\text{cm}$, without taking the accuracy of the sensor cell constant into account. All MT conductivity meters have a resolution of 0.01 $\mu\text{S}/\text{cm}$ or better in that range. The general accuracy of the instrument's sensor input is 0.5% - calculated to $\pm 0.07 \mu\text{S}/\text{cm}$ at 1.3 $\mu\text{S}/\text{cm}$ - well within the limits of compliance with the norm.

b) Sensor calibration and verification of the conductivity cell constant

Sensor calibration is indispensable for a reliable conductivity analysis, and hence essential to ensure the reliability and quality of the manufactured products. Calibration could be defined as establishing the difference between what should be measured and what a sensor really measures. For a conductivity sensor, calibration means determining its cell constant, which is a factor that considers the geometrical characteristics of a conductivity sensor.

The conductivity cell constant can be defined either by the user through a calibration using a standard solution of known conductivity, or by the manufacturer, who provides the cell constant in a certificate. Such a certified cell constant can be entered directly into the instrument what makes an additional calibration obsolete. For low conductivities the usage of a sensor with a certified cell constant is strongly recommended. The equipment used, as well as environmental controls yield a cell constant with a more accurate value than a sensor which is calibrated in a lab by the end-user. In addition, the simple entry of the cell constant makes the process much easier for the user than an additional calibration.

USP requires that the value of this cell constant must be known with an accuracy of $\pm 2\%$ of the stated value. Compliance with this standard is ensured via regular sensor verification readings. A simple measurement of a reference solution of known conductivity is enough to assess the accuracy. It is crucial that the temperature compensation is deactivated and this reading is compared to temperature-conductivity tables (Table 1 is shown as an example) provided on the bottle labels and sachets of the conductivity standards.

Temperature (°C)	18	20	23	25
Conductivity ($\mu\text{S}/\text{cm} \pm 1\%$)	8.56	8.97	9.59	10.00

Table 1. METTLER TOLEDO conductivity standard for 10 $\mu\text{S}/\text{cm}$ at temperature from 18 to 25 °C.

The sensor used must be accurate in a very low conductivity range and thus has a low nominal cell constant. Usually its shaft material is made of stainless steel or titanium, so as to be able to measure low conductivity values.

MT recommends using the following combinations of conductivity sensors and instruments:

1. InLab 741, InLab 741-ISM or InLab Trace (digital sensor) sensors for SevenExcellence and SevenCompact instruments.
2. InLab 742 or InLab 742-ISM sensors for Seven2Go Pro and SevenGo Duo Pro instruments.

The above listed sensors are delivered with a certified cell constant. Digital and ISM sensors have this value stored in the sensor's memory chip, which is transferred to the instrument automatically. For non-ISM versions of InLab 741 and InLab 742 the cell constant can be manually entered into the instruments.

c) Use of non-temperature compensated conductivity readings

Conductivity measurements are very temperature sensitive. In order to account for the impact of temperature variations on the conductivity value, many instruments apply a correction factor. This factor normalizes the conductivity value, mathematically adjusting the reading to a reference temperature (normally to 25 or 20 °C).

This normalization is typically achieved by using an algorithm and a temperature probe, which is usually incorporated in the conductivity sensor. The algorithm is embedded in the instrument's system and calculates the conductivity at nominal temperature using the correction factor. The accuracy of this algorithm may change depending on the sensor (it can be linear or non-linear). In order to perform all measurements in the same way, regardless of the accuracy of the algorithm of the sensor used, the temperature correction must be disabled in the instrument's setup.

d) Conductivity standard solutions used for calibration and verification of the cell constant

A major USP requirement is that the cell constant must be known within $\pm 2\%$. As mentioned above, the cell constant is either known and certified, or the sensor must first be calibrated in a standard solution in order to determine its value. In a second step, the value of the cell constant needs to be verified for all sensors (certified and non-certified).

One very common error is to perform the calibration, in the case the user carries it out, with a very low conductivity standard solution. Standards below and including 10 $\mu\text{S}/\text{cm}$ are not suitable for an accurate calibration due to their instability, introducing error into the solutions themselves. The conductivity value of these standards increases quickly due to the absorption of atmospheric carbon dioxide, which leads to erroneously high conductivity values. It is advisable to use standards with slightly higher conductivity values for calibration so as to avoid this problem. MT recommends calibrating the sensor using the 84 $\mu\text{S}/\text{cm}$ standard solution.

Once the sensor is calibrated, a subsequent verification measurement of conductivity is performed. It is advisable to do the verification measurement in a low conductivity standard solution (e.g. 10 $\mu\text{S}/\text{cm}$) since the conductivity of samples like PW and WFI samples is within this range. The sensor should first be rinsed with deionized water, then with the standard. In order to avoid contact with air as much as possible, the reading should be taken with the sensor directly in the bottle or using a flow-cell. In both cases the solution has to be discarded afterwards. The reading has to be within $\pm 2\%$ of the solution's tabled conductivity value for the measured temperature.

2. Procedure

In order to measure the quality of PW and WFI through conductivity readings, a three-stage procedure must be followed:

a) Stage 1

Firstly, a water temperature measurement and a non-temperature compensated conductivity reading are performed. USP <645> requires a precision of ± 2 °C in temperature measurement. The temperature probe input of the MT Seven Series pH instruments has a limit of error of ± 0.1 °C. Both temperature probes that are built into MT InLab® conductivity electrodes as well as the external ones (separate InLab® temperature probes) have a tolerance of ± 1 °C or lower, perfectly in compliance with the norm.

The measured conductivity value is compared to a Temperature/Conductivity Limits table (Table 2). If the measured temperature value is not on the list, the next lower temperature must be taken in order to define the conductivity limit. Interpolation should not be performed.

If the measured conductivity value does not exceed the corresponding conductivity limit value on the table, the test is complete. If it is higher than the table value, then it is necessary to proceed to Stage 2.

It is recommended that the measurement is performed at-line using a sample bottle or beaker.

Temperature (°C)	Conductivity Limit (µS/cm)	Temperature (°C)	Conductivity Limit (µS/cm)
0	0.6	55	2.1
5	0.8	60	2.2
10	0.9	65	2.5
15	1.0	70	2.5
20	1.1	75	2.7
25	1.3	80	2.7
30	1.4	85	2.7
35	1.5	90	2.7
40	1.7	95	2.9
45	1.8	100	3.1
50	1.9		

Table 2. Stage 1 – Conductivity Limits as a Function of Temperature.

b) Stage 2

As a first step, a sample of water with a volume of at least 100 mL is taken and transferred to a container. Before measuring the conductivity, the temperature of this water sample must be stable at $25\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$, so consider a temperature adjustment and maintenance. Then, the sample is stirred, and hence is equilibrated with air.

No further conductivity readings should be taken until the conductivity value remains stable, keeping the same value over a period of 5 minutes (with a possible variation up to $0.1\text{ }\mu\text{S/cm}$). At this time, the water sample is saturated with air due to the absorption of atmospheric carbon dioxide.

In case the new conductivity reading does not exceed $2.1\text{ }\mu\text{S/cm}$, the test is successful. If the water test fails, Stage 3 needs to be performed so as to verify the water quality.

c) Stage 3

In order to adjust the ionic strength, saturated KCl is added to the previous sample (0.3 mL of KCl per 100 mL of water sample) and then pH is measured. This test should be done approximately 5 minutes after the end of Stage 2, and as before, the temperature needs to be kept relatively constant at $25\text{ }^{\circ}\text{C} \pm 1\text{ }^{\circ}\text{C}$ throughout the development of the measurement.

If at that pH, the conductivity measured at Stage 2 does not exceed the conductivity limit in Table 3, the tested water sample complies with USP requirements.

pH	Conductivity Limit ($\mu\text{S/cm}$)	pH	Conductivity Limit ($\mu\text{S/cm}$)
5.0	4.7	6.1	2.4
5.1	4.1	6.2	2.5
5.2	3.6	6.3	2.4
5.3	3.3	6.4	2.3
5.4	3.0	6.5	2.2
5.5	2.8	6.6	2.1
5.6	2.6	6.7	2.6
5.7	2.5	6.8	3.1
5.8	2.4	6.9	3.8
5.9	2.4	7.0	4.6
6.0	2.4		

Table 3. Stage 3 – Conductivity Limits as a Function of pH.

It is important to note that in Table 3 the pH range is 5 to 7. If the measured pH is outside of this range, or the measured conductivity is higher than the conductivity permissible at that pH value (on Table 3), then the water sample tested is not compliant with the norm.

4. Conclusion

Compliance with USP <645> norm is required for many applications related to the pharmaceutical industry. With a 3-step procedure, it is possible to introduce errors as tables are manually referenced, leading to inaccurate results or failed audits. Therefore, care must be taken.

A deciding factor in reducing measurement inaccuracies is choosing the right equipment. Picking the most adequate conductivity probe with a certified cell constant, along with the suitable conductivity standards for calibration and verification are key to an accurate and reliable measurement. Additionally, an appropriate instrument (especially equipped with predefined methods) aids in meeting with strict regulations, ensuring fast and accurate results in your testing. METTLER TOLEDO advises to take these factors into account and conduct your next conductivity measurement in accordance with these recommendations.

5. References

- [1] United States Pharmacopeia, 40th Edition. Physical Test Method <645> "Water Conductivity".
- [2] Anthony C. Bevilacqua (1999). Harmonization of Conductivity Tests for Pharmaceutical Waters. A portion of this paper was presented at the Parental Society meeting on September 14, 1999 in London, England. Thornton Inc.
- [3] John J. Barron and Colin Ashton. Conductivity Measurement – Do You Comply With the Pharmacopeias?. Technical Services Department, Reagecon Diagnostics Ltd, Shannon Free Zone, Country Clare, Ireland.
- [4] METTLER TOLEDO. Selected applications: 21 METTLER TOLEDO methods for SevenExcellence. SBU pH Lab, Mettler-Toledo GmbH - Analytical. Schwerzenbach, Switzerland.
- [5] METTLER TOLEDO. White Paper: perform your next pH measurement in compliance with USP <791>. SBU pH Lab, Mettler-Toledo GmbH - Analytical. Schwerzenbach, Switzerland.

www.mt.com

For more information

METTLER TOLEDO Group

Laboratory Division
Local contact: www.mt.com/contacts



Subject to technical changes
© 10/2017 METTLER TOLEDO. All rights reserved
30431332
Marketing SBU pH Lab / MarCom Analytical