Conductivity Measurement – Do You Comply With the Pharmacopoeias?

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Abstract

Although the water conductivity monographs of Ph. Eur. and USP have been in place for several years, there is still considerable confusion within the pharmaceutical industry on their interpretation and implementation. This paper gives a detailed interpretation of these regulations, including official clarification of the Ph. Eur conductivity monograph that these authors have received from the European Directorate for the Quality of Medicines. As well as covering the measuring equipment and test methodology required for compliance, this paper also explains why the use of low-level, aqueous conductivity standards is essential for regulatory compliance.

1 Introduction

Since 1996, the European Pharmacopoeia (Ph.Eur.) and United States Pharmacopeia (USP) have specified conductivity as a key parameter for assessing the quality of purified water and Water For Injection (WFI) used in the manufacture of pharmaceutical products. Until recently, there were major differences between the Ph. Eur. & USP sections on conductivity measurement. Recent editions of Ph. Eur. have been brought broadly in line with the conductivity requirements of USP, due to the harmonisation efforts of the Pharmaceutical Discussion Group (PDG). This allows pharmaceutical companies to use the same test procedure to comply with the conductivity testing requirements of both Ph. Eur and USP. However, the current edition of Ph. Eur. (Ed. 5.4)[1] still includes extra stipulations that are not covered in USP 29[2] or its predecessors.

These authors regularly communicate with personnel of pharmaceutical companies who are responsible for ensuring that their organisation's conductivity measurements comply with the Pharmacopoeias. Many of these pharmaceutical contacts are unsure of how these sections of the Pharmacopoeias should be interpreted and what equipment and procedures they must have in place for compliance. As a result of these discussions, these authors sought clarification from the European Directorate for the Quality of Medicines (EDQM) on the official interpretation of the Ph. Eur. requirements governing conductivity measurements.

This paper gives a detailed description of the Pharmacopoeial requirements for conductivity measurement, including the interpretation received from the EDQM[3,4]. Guidance is given on the equipment and test methods required from pharmaceutical companies to ensure that they can demonstrate compliance with these regulations. This will enable pharmaceutical companies to identify if their conductivity measurements comply with the Pharmacopoeias and what changes, if any, they need to make to their systems to demonstrate compliance.

2 Pharmacopoeial Requirements

Both Pharmacopoeias specify three methods for conductivity testing of purified water and WFI:
Stage 1: In-line testing
Stage 2: Off-line (laboratory) testing, whilst stirring the sample to ensure that it becomes saturated with atmospheric carbon dioxide, resulting in a stable conductivity value
Stage 3: Off-line pH and conductivity testing after addition of potassium chloride to the sample.

Stage 3 testing is only performed on samples that have failed the Stage 2 test. High quality purified water is essential for the manufacture of

Criteria	Requirement
Calibration of instrument (with the cell disconnected)	Performed using certified resistors of accuracy ± 0.1% of stated value
Instrument resolution	Minimum 0.1 µS/cm
Use of temperature compensation	Function must be disabled
Stage 2 test method	Agitate sample at 25°C ± 1°C. Record the value when the conductivity changes by less than 0.1 µS/cm per 5 minutes. The conductivity must be less than 2.1 µS/cm
Cell constant verification	Must be known to ± 2%

Table 1: Conductivity Testing Requirements Common to Ph. Eur. Edition 5.4 and USP 29

Criteria	Ph. Eur. Requirement	USP Requirement
Instrument accuracy (excluding cell) – determined using certified resistors	Test required, but accuracy not specified	± 0.1 µS/cm
Cell constant verification	Using conductivity standards less than 1,500 µS/cm. Verification of cell constant performed at 25°C ± 1°C	With a conductivity standard or by comparing reading with certified cell
System accuracy (instrument and cell)	3% plus 0.1 µS/cm in certified conductivity standard. Can be done by comparison with certified cell for Stage 1 only	No similar test specified

Table 2: Differences between Ph. Eur. Edition 5.4 and USP 29 Requirements

most pharmaceutical products and so most pharmaceutical companies build in significant safety factors on the performance indicators of their water purification system. Corrective actions are usually instigated well before samples reach the pass/fail limit for Stage 2. For this reason, Stage 3 testing is rarely performed. This paper concentrates on Stage 2 testing, as this is the method most commonly used in pharmaceutical laboratories.

The conductivity criteria common to Ph. Eur. and USP are summarised in Table 1. It should be noted that, whilst there have been changes to the Pharmacopoeias to harmonize their conductivity measurement requirements, there are still some differences between Ph. Eur. and USP – these are summarised in Table 2.

3 Complying with the Pharmacopoeias

3.1 Basic System Specification

Initial investigation of the Pharmacopoeias' Stage 2 criteria means that the measuring system should include the following components:

A waterbath – to ensure that cell constant verification and sample measurement is carried out at 25°C ± 1°C.

An overhead stirrer – to agitate the samples during measurement. Any components that are in contact with the samples should be made of materials that will not affect the samples' conductivity (e.g. stainless steel or plastic). Overhead stirrers are preferable to submersible magnetic stirrers, as the latter's magnetic field may interfere with the performance of the conductivity cell. The stirring speed should be sufficient to draw atmospheric carbon dioxide into the sample; but not excessive, as this may result in air bubbles being drawn into the conductivity cell, resulting in spurious readings.

A conductivity meter that allows its temperature compensation function to be disabled, with resolution of at least 0.1 µS/cm and accuracy of at least ± 0.1 µS/cm for its lowest measuring range.

A conductivity cell with an integral temperature sensor. A cell and meter that can measure conductivity and temperature is the most obvious means of complying with the requirement that these parameters are measured simultaneously. A cell with nominal cell constant of 0.1 or 0.01cm^{-1} should be used, to ensure that the samples' conductivity is within the linear response range of the cell[5].

A certified, traceable conductivity standard for verification of the cell constant. Ph. Eur. requires this standard to have a value below 1,500 µS/cm. However, cells that are capable of accurate low conductivity measurement have an

upper limit to their linear response range of 200 - 300 µS/cm. The conductivity standard must be within the cell's linear response range. 147µS/cm is the most commonly used standard for this application.

3.2 Accuracy Requirements

Most of these authors' discussions with pharmaceutical contacts concentrated on the interpretation of the requirements for the cell constant verification check (Ph. Eur and USP) and the system calibration check (Ph. Eur. only). Consequently, the authors sought official guidance on the interpretation of these requirements from the European Directorate for the Quality of Medicines (EDQM). The EDQM[3] response and these authors' guidance on its implementation is given in this section.

3.2.1 Cell Constant Requirements of USP and Ph.Eur.

These sections of both Pharmacopoeias are vague. These authors strongly urge that they be re-written using precise language, preferably using terminology as defined by VIM[6].

The USP requirement reads: "The conductivity cell constant … must be known within ±2%. The cell constant can be verified directly by using a solution of known conductivity, or indirectly by comparing the instrument reading taken with the cell in question to readings from a cell of known or certified cell constant."

The Ph. Eur. requirement reads: "…cell constant: within 2% of the given value determined using a certified reference solution with conductivity less than 1500 µS/cm"

These authors and most of their contacts within the pharmaceutical industry had interpreted these Pharmacopoeial sections as relating to calibration – i.e. assignment of the cell constant. The USP states that the cell constant must be "known within ±2%". This suggests that Uncertainty of Measurement associated with the cell constant assignment must be less than 2%, as Uncertainty of Measurement is the only means by which the error associated with the cell constant assignment can be quantified.

The clarification that EDQM gave on this section of Ph. Eur. was[3] "… the cell manufacturer's certified cell constant can be used in calculations if it is within 2% of the cell constant obtained by measuring the cell's response on a certified reference solution. If this condition is not met then the cell must be re-calibrated". This means that this section of Ph. Eur. relates to **verification of the cell constant value** and not to calibration – i.e. traceable assignment of the cell constant.

Although these authors have not received a similar, official interpretation of the conductivity section of USP, they believe that the clarification received from EDQM can be applied to USP for two reasons:

- The relevant sections of Ph. Eur and USP are being harmonized under the auspices of the PDG. Although the wording of Ph. Eur. and USP differs slightly, they are describing the same requirements.
- The chairman of the USP Pharmaceutical Water Expert Committee has written a paper[7] that includes a description of how compliance with the USP requirements is met through verification of the cell constant within 2%, rather than through calibration. Although this is not an official interpretation of the USP, it does come from a noteworthy source.

The EDQM response continued "I understand that it is usual practice for the cell supplier to calibrate and for the user to check the value periodically. If it falls outside the 2% tolerance then the cell is recalibrated (often by the supplier". This arrangement is common-place for in-line conductivity cells; but these authors are not aware of a manufacturer of laboratory conductivity cells that provides a cell-constant re-certification service. This service is not necessary, as users of laboratory conductivity systems can readily perform a traceable calibration by using a certified, traceable conductivity standard solution.

3.2.2 System Calibration Requirement of Ph. Eur.

The section of Ph. Eur. governing system calibration relates to the conductivity cell and instrument (i.e. the complete measuring system) and must meet two criteria:

- "against one or more suitable certified standard solutions"
- "accuracy within 3 per cent of the measured conductivity plus 0.1µS/cm"

These authors sort clarification from the EDQM on what constituted a "suitable certified standard

solution". They specifically asked if such a standard must be of similar conductivity value to the samples and must be of aqueous matrix, as the samples are aqueous. The EDQM replied that the standard must be of similar conductivity value to the samples and that they were not sure of the matrix requirement; but "would expect that the use of aqueous solutions is necessary". The system calibration check should show that the measuring system will provide suitably accurate measurements on aqueous samples. Consequently, these authors recommend that only aqueous conductivity standards should be used, as measurements of non-aqueous standards will not give an indication of the system's ability to measure aqueous samples correctly.

As part of the Stage 2 test methodology, the samples are agitated so that their absorbed carbon dioxide content is equilibrated with the atmosphere. The absorption of atmospheric carbon dioxide will increase the conductivity of the samples by 0.8 – 1.2µS/cm, depending on the local conditions[8]. As the maximum permissible conductivity for Stage 2 testing is 2.1µS/cm at 25°C, samples passing this test will have a conductivity value of 0.8 – 2.1 µS/cm at 25°C.

The ideal certified standard solution for the system calibration check will have the following properties:

- Similar conductivity value to the samples – i.e. 0.8 – 2.1 µS/cm at 25°C.
- Aqueous matrix
- Traceable to Primary Standards
- Proven Stability – concerns have been raised over the availability of stable low-level conductivity standards[9].

Reagecon's 1.3µS/cm conductivity standard satisfies all of these criteria. It is the only aqueous conductivity standard in the samples' conductivity range. Reagecon's traceability and uncertainty of measurement claims for their assay of this standard are guaranteed by their ISO 17025 accreditation[10] and details of the stability studies performed on this conductivity standard have been published[11].

The authors also received clarification from the EDQM that the certified standard solution's specification can be added to the 3% plus 0.1µS/cm to give the allowable limits on the system accuracy. This means that if Reagecon's 1.3µS/cm conductivity standard is used for the system calibration check then readings of 1.3 ± 0.189µS/cm would meet the requirements of the Ph. Eur., as shown in Table 3.

Acceptance Limit Component from Ph. Eur & EDQM clarification	Value (µS/cm)
3% of value of standard	± 0.039
"plus 0.1µS/cm"	± 0.100
Specification limits of Reagecon's 1.3µS/cm Conductivity Standard	± 0.050
Total Acceptance Limit	± 0.189 **i.e. 1.111 – 1.489**

Table 3: Acceptance Limits for the Ph. Eur. "System Calibration" check Performed Using Reagecon's 1.3µS/cm Conductivity Standard

3.2.3 Use of Conductivity Standards to Comply with Ph. Eur.

These authors queried if both the cell constant verification and the system calibration checks could be satisfied simultaneously if a reading of within 2% of the certified value of a 1.3µS/cm conductivity standard was obtained. The EDQM response was "it seems acceptable to use the same reference solution to verify (at the same time) cell constant and system suitability"[3].

Given this response, these authors recommend users to check the performance of their conductivity systems using Reagecon's 1.3µS/cm conductivity standard. The result obtained in this Control Standard will determine the appropriate course of action:

- If the result is within 2% of the certified value of the Control Standard then no further action is required, as both the "system calibration" and "cell constant verification" criteria have been met.
- If the result is not within 2% of the certified value of the Control Standard, but is within the range 1.111 – 1.489µS/cm then only the "system calibration" criteria has been met. The "cell constant verification" check should be performed using a higher value conductivity standard, e.g. 147µS/cm. If the measuring system passes this test then both checks will have been passed and no further action is required. If the measuring system fails this test then the cell constant should be re-assigned and the "system calibration" check should be repeated with the 1.3 µS/cm conductivity standard.
- If the result is outside the range 1.111 – 1.489µS/cm then the cell constant should be assigned using a higher value conductivity

standard, e.g. 147µS/cm, and the "system calibration" check should be repeated with the 1.3 µS/cm conductivity standard.

It is not acceptable practice to use the same conductivity standard for assigning the cell constant and for the "system calibration check". This practice would not demonstrate the validity of the assigned cell constant. Control Standards must be independent from Calibration Standards, as they are not only used to show that the equipment is functioning correctly; but also that the calibration and test method have been performed correctly.

3.2.4 Measuring System Implications of the Accuracy Requirements

The Pharmacopoeial accuracy requirements place additional burdens on the equipment used for measuring conductivity. A measuring system that only just meets the basic specification requirements of the Pharmacopoeias will not be able to comply with these accuracy requirements. Special attention must be taken with the following areas:

Temperature control and measurement. Aqueous conductivity standards' and samples' conductivity changes by approximately 2% per 1°C change in temperature[12]. This means that a 1°C error in temperature measurement will result in a 2% error in conductivity measurement. Hence, temperature measurement and control must be significantly better than the ± 1°C specified in the Pharmacopoeias to comply with the cell constant verification and system calibration accuracy criteria.

Conductivity Standards' Specification. An accurate conductivity standard must be used for verifying the cell constant. Some manufacturers claim that conductivity standards with a specification of ± 2% meet the Pharmacopoeial requirements. The use of such low specification standards will lead to frequent failure of the cell constant verification check, as their specification uses up the allowable tolerance on the cell constant verification test. Conductivity standards with a specification of ±1% are readily available and should be used for this purpose.

Conductivity Standards' Matrix. Although the EDQM response did not categorically state that non-aqueous conductivity standards should not be used for the system calibration check, the use of non-aqueous conductivity standards should be avoided. These standards can have a temperature coefficient of variation in excess of 7% per °C, requiring extremely exacting temperature control and measurement accuracy to comply with the Pharmacopoeias.

Linear Response. High quality conductivity meters and cells must be used, as they must provide a linear response in the samples' measurement range.

4 Full Audit-Compliance of Conductivity Measurements

As is the case with all analytical measurements that affect the quality of pharmaceutical products, conductivity measurements are governed by regulations that require appropriate Equipment Qualification, Method Validation, Quality Assurance and Quality Control to be performed. A detailed description of the complete requirements of each of these areas is beyond the scope of this paper. However, guidance is given on their application to conductivity measurements and the fundamental role that suitable conductivity standards play in these activities.

4.1 Method Validation

The conductivity test methods described in the Pharmacopoeias have been validated prior to their inclusion in these publications. Consequently, pharmaceutical companies are not required to fully validate their conductivity test methods. However, they are required to **verify** their compliance with the Pharmacopoeial method performance capabilities prior to using a new method for sample analysis.

4.1.1 Verifying Compliance with Ph. Eur.

These authors sought confirmation from the EDQM on the extent of the assessment required to verify that a pharmaceutical company's conductivity measurement method complied with the requirements of the Ph. Eur. The EDQM response was:

"The methods included in the monograph are considered as validated. It is sufficient to show that the system suitability criteria described in the monograph are fulfilled"[4].

The system suitability criteria cited by the EDQM is described as a 'system calibration check' in the conductivity monograph of the Ph. Eur. Performance of this check requires the use of a suitable, low conductivity standard solution, as described in Section 3.2.2.

4.1.2 Verifying Compliance with USP

The most significant difference between the conductivity monographs of Ph. Eur. and USP is that USP does not include system suitability criteria. This stipulation of Ph. Eur. provides an obvious means of demonstrating compliance that is lacking for USP.

In the absence of a system suitability check in the USP conductivity monograph, these authors recommend that the system calibration check of the Ph. Eur, is followed. Both Pharmacopoeias are describing the same test regime, so this will demonstrate compliance with the cGMP requirement that "the suitability of all testing methods used shall be verified under actual conditions of use"[13].

4.2 Equipment Qualification

The initial stages of Equipment Qualification cover the documented measures that must be taken to ensure that analytical instruments are specified, selected and installed so that they are capable of producing measurements that are fit for their intended purpose. The Performance Qualification (PQ) phase covers the measures that are taken to ensure that the instrument's performance remains fit for its intended purpose throughout the instrument's entire operational life[14].

Before purchasing new conductivity measuring equipment, pharmaceutical companies should ensure that their equipment vendor can provide Installation Qualification (IQ) and Operational Qualification (OQ). OQ demonstrates that, prior to being put into service, the equipment is capable of producing measurements that are fit for its intended application. OQ must include a test measurement on a low-level, aqueous standard, as this is the only means of showing that the equipment's performance is fit for purpose. It should be verified that the vendor's OQ protocol includes this test.

The main tools of PQ are Control Standards, as they provide an holistic check of the complete measuring system. For the Control Standards to provide a meaningful indication of the measuring system's ability to provide reliable sample results, they must be of similar value and matrix to the samples. Hence Reagecon's 1.3 µS/cm Conductivity Standard is ideal for this purpose.

4.3 Performance Checks

Suitable quality control performance checks must be in place for all analytical measurements to provide confidence in the samples' test results. The most commonly used tools for this purpose are Control Standards.

The system calibration check outlined in Ph. Eur. is a Control Standard check. The acceptance limits, described in Ph. Eur. and clarified by EDQM, should be incorporated into pharmaceutical companies' conductivity test procedures. Although the USP Water Conductivity Monograph does not specify a Control Standard check, such a check is required to comply with the cGMP requirement that suitable quality control measures are in place for all analytical measurements.

4.3.1 Frequency of Control Checks

The frequency of performance of the Control Standard check depends on a number of factors:

- The complexity of the test procedure
- The robustness of the test method
- The criticality of the test result

Although the conductivity test methods used by pharmaceutical companies are straightforward and the test method may be relatively robust, the criticality of these test results is very high. Consequently, frequent performance of the Control Standard check is required.

Some pharmaceutical companies only perform Control Standard checks after each calibration of their conductivity system. A Control Standard check performed after a calibration verifies that the calibration has been performed correctly. However, this alone does not meet the purpose of the Control Standard checks, i.e. to demonstrate control over all of the samples' conductivity measurements. A Control Standard check should be performed with every batch of samples being analysed. If an acceptable reading is obtained for the Control Standard then this shows that the test method, measuring equipment, system calibration, control of the test environment and the analyst are all performing to the level required for confidence in the samples' analysis.

Control Standards are also a useful tool in confirming that analysts have been suitably trained to perform a test method. Analysts should not perform a test method on samples until they are able to consistently meet the

acceptance limits required for the Control Standard test.
Frequent use of Control Standards will increase the cost of analysis. However, this is far outweighed by the financial and regulatory implications of incorrect conductivity results generated by a testing regime that does not include adequate quality control measures.

5 Recommended Improvements to the Monographs

The Pharmacopoeial conductivity monographs are currently being harmonised under the governance of the Pharmaceutical Discussion Group (PDG), with Ph. Eur. co-ordinating this activity.

These authors strongly urge the PDG to ensure that the system calibration check carried in Ph. Eur. is transferred to USP. Considerable method validation efforts were undertaken to support the inclusion of the conductivity measurement method in USP. The value of these validation efforts are diminished without a system suitability check, as users of the method cannot readily assess if their own analytical performance is acceptable.

These authors regularly discuss the monographs covering conductivity measurement with their contacts within the pharmaceutical industry and have met with a range of interpretations of how the monographs should be implemented. This ambiguity is highlighted by the EDQM reply to the authors' query on the required matrix for conductivity standards: "I am not sure of the answer to this but I would expect that use of aqueous solutions is necessary".

Whilst the monographs should not be unnecessarily prescriptive, they do need to be revised to give more clarity. The ultimate objective of the Pharmacopoeias is to safeguard human health – this cannot be achieved unless their meaning is clear. The monographs' authors are to be commended in avoiding the unnecessary use of jargon. However, ambiguous statements such as "the cell constant … must be known within ± 2%" do not serve the purpose of the Pharmacopoeias.

6 Conclusion

Many pharmaceutical companies are unsure of how the Ph. Eur and USP sections governing conductivity measurement should be interpreted and implemented. The detailed explanation given in the paper gives clear guidance on how Pharmacopoeial compliance can be attained and includes an explanation of the official clarification of the Ph. Eur. that these authors have obtained from the EDQM.

As well as covering the basic equipment and methodology required for Pharmacopoeial compliance, attention must also be paid to the equipment qualification and quality control measures that are required to comply with regulations governing pharmaceutical analytical measures. The key tool required for effective equipment performance qualification and test method performance checks is a suitable conductivity standard. Such a standard must be aqueous; of low conductivity; certified as being traceable to Primary Standards and must have proven stability. Reagecon's 1.3 µS/cm Conductivity Standard meets all of these criteria and so is a key component of any compliant pharmaceutical conductivity measuring system.

7 References

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* These papers form part of a comprehensive series that the authors have written covering all of the practical requirements for accurate conductivity measurement. These papers and the authors' book, "A Practical Guide to Accurate Conductivity Measurement" are available via Reagecon's website - www.reagecon.com.

Biographical Notes:

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Colin Ashton has worked in the Reagecon group since 1994 and is currently Head of the Chemical Metrology Department. A graduate of the University of Southampton, he has developed particular expertise in the development, stabilisation, manufacture and validation of cation, anion and electro-chemical standards. He has particular scientific interest in all aspects of conductivity analysis and has lectured and published on several areas of this field.

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