Reagecon Conductivity Standards –

Context, Justification, Features and Benefits

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Abstract: *Over the last 140 years several groups of researchers have carried out highly significant work on the development and enhancement of conductivity standards. Most of this work has been applied to either primary standards or secondary standards that lack fitness for purpose in a real life commercial environment. This paper summarises extensive work carried out on the development of fit for purpose secondary conductivity standards using unique technology which has been developed in our laboratory. We present the market justification and context within which the products were developed and present features and benefits on this unique family of products supported by comparative data. Critically, the justification for the products is applicable from a metrological and GLP standpoint to all secondary standards.*

1.1 Introduction and Context

The development, evolution and state of the art of conductivity standards from 1869 to the work of this author will be presented by Barron and Ashton in their forthcoming book(1). In the intervening period of 140 years or so outstanding scientific contributions have been made by several groups and individuals.[a,b]

Several advances in knowledge and technology have occurred, including reappraisal of existing knowledge with the view to improving the assignation of measurement uncertainty to these standards. During that time changes have also occurred in the units and measurements scales to include the following:

- temperature
- volume
- molar mass
- resistance

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[a] These workers include Kohlrausch and his co-workers in Germany and Switzerland between 1869 and 1900; Henry and Elizabeth Parker in the Leeds and Northrup company in Philadelphia in 1924; the extensive work on all aspects of conductivity by Grinnell Jones and his co-workers in Harvard in the 1930s and in particular the work of Jones and Bradshaw (1933) and Jones and Prendergast (1937); Theodore Shedlovsky on secondary standards in 1933 and in several subsequent publications up to the 1950s; Wu et al in the 1990s and Spitzer and her co-workers in the 2000s followed by the work on Barron and Ashton in this laboratory from 2004 to the present time. (see bibliography)

[b] Almost all of the work prior to that of Barron and Ashton has focused on primary standards and was carried out in a research environment. The work of Barron and Ashton is presented in a series of a dozen or more papers and a text book which will be published in late 2010.

- concentration

All of these factors have contributed to lack of certainty of the accuracy of such standards and have obfuscated clear thinking on the fitness for purpose and relevance of conductivity standards. They have also obfuscated a clear understanding of their ever increasing relevance particularly relating to developing the science of Metrology. Most workers have focussed on improvement in the accuracy and uncertainty computation pertaining to primary conductivity standards and most of the work has been carried out in institutions that focus on the use or production of primary standards. Although such standards continue to be highly relevant and essential,(1) the production and use of fit for purpose secondary standards for everyday use in a real life commercial environment has been neglected. Such neglect has emanated from a number of converging factors as follows:

1. Most workers have focussed on the use of conductivity standards for the calibration or re-calibration of the measuring cell. Most of this work has emanated from theoretical undertakings, is performed in respected institutions but is limited in it's day to day use or commercial value. Few have focussed on an equally important, but much more widespread use of the standards as a control material for each test carried out in line with the principles of metrology and good laboratory practice.(2)
2. A large proportion of work carried out has focussed on the use of conductivity for once off studies on the properties of electrolyte solutions, in particular the development of modern theory pertaining to ionic interaction, electrolyte behavior, ionic interaction, ion mobility or other considerations of interest to physical rather than analytical chemists and as a powerful and useful methodology for determining ionic dissociation upon which large numbers of chemical reactions depend. Such work, although critical, is carried out under controlled conditions in research laboratories where the standards can be produced fresh as often as daily under standardised and controlled conditions which bear no resemblance to the use of conductivity standards as either control or calibration materials under routine test conditions where conductivity measurement is used as an analytical tool.
3. Production of primary standards rarely focuses on measurement uncertainty as a function of time that is realistic in the context of the production, transport and use of such standards under commercial or routine conditions. Such standards are rarely suitable for use as secondary or working standards.

4. Work that has focussed on primary conductivity standards has been subject to widespread statistical and mathematical modelling. Such modelling is entirely appropriate for work on primary standards or for the use of such standards in work relating to electrolytic or ionic theory. However, such modelling is not always fit for purpose in the production or use of secondary or working standards and can lead to a lack of understanding and confusion by the users of such standards.

5. Almost all of the work previously carried out on conductivity standards has focussed on their use to calibrate conductivity cells. The benefits of using these standards and in particular secondary or working standards as control material has been ignored. The advent of the science of chemical metrology has given renewed emphasis to the use and necessity of controlled materials. The benefits of such controls cannot be overstated. Although stated elsewhere by this author and others,[3, 4] because of its significance, such a statement needs reiteration. As with all analytical standards or reference materials, conductivity standards should fulfil the following criteria

    - Provide traceability
    - Demonstrate the accuracy of results
    - Calibrate the equipment and methodology
    - Monitor the user performance
    - Validate the test
    - Facilitate comparability, that is to ensure that when the correct procedures have been followed, the same analysis of the same materials will produce results that agree with each other whenever they are performed
    - Such materials must also be able to fulfil the criteria required for quality control, accreditation and proficiency testing where appropriate[3]. Standard and reference materials should be produced and characterised in a technically competent matter, should be homogenous, stable, certified and have available a known uncertainty of measurement as a function of time[4]. In addition to the context of metrology such secondary standards are relevant relating to regulatory requirements, quality control, accreditation, and good laboratory practices as outlined in the bullet points above.[5, 6, 7]

6. Secondary or working standards need to be affordable, widely available and certified. The production, stability, assignation of uncertainty as a function of time and commercialisation of an extensive range of fit for purpose conductivity standards that includes low level

standards has occupied the time and resources of the author's laboratory for several years. It encompasses the use of unique proprietary technology. However, because of the seminal nature of some of the work carried out and published pertaining to conductivity standards by other authors and in order to provide meaningful context for the uniqueness and novelty contained in the work of this author, it is necessary to present an historical treatise of the progression of published work to date on conductivity standards. This work is outside the scope of this document but is presented elsewhere(1). Such review will also add context to both the benefits and efficiencies of the state of the art, up until the inventions presented by this author, from a metrological standpoint.

7. In the context of normal commercial or routine use conductivity standards (or any other standards) need to be rugged, have extensive shelf life, be fit for purpose and have their uncertainty of measurement characterised as a function of their shelf life. None of the published work to date has dealt with these considerations and such considerations form a core element of the novelty, innovativeness and scope for commercialisation of our work. The rapid commercialisation and demand for the products and their use in over 2000 laboratories worldwide since their introduction is testament to the market requirement for such products and the market gap that they fill.

The measurement of conductivity is carried out in a wide variety of industries and applications, some of which are covered in this work and more specifically the measurement of low-level conductivity is carried out in a wide range of industries, e.g. power generation, pharmaceutical and semi-conductor manufacture and is principally performed on aqueous samples. In such instances, critical decisions are made based upon these conductivity readings and so it is essential that analysts can not only achieve the correct conductivity test results, but also prove the validity of their results.

1.2 Justification

As is the case with all measurements in analytical chemistry, the last 20 years or so has seen a massive proliferation in the requirement of both numbers and accuracy of qualitative, semi-qualitative and qualitative measurements. This requirement includes conductivity measurement and makes a necessity for "fit for purpose" secondary standards an imperative. Broadly, this requirement has been driven by the following factors

1. More accurate apparatus, aided by better technology.
2. More regulation to include for example
   - USP, EP, JP and other pharmacopoeias
   - ISO17025 and equivalent accreditations
3. Growing worldwide interest and awareness of metrology to include traceability, comparability and measurement uncertainty by way of examples.
4. Greater need for products such as Ultrapure Water with the advent of industries such as the semi-conductor and biopharmaceutical industries.
5. Proliferation of technical industries such as the pharmaceutical industry that either uses or produces high quality waters to include water for injection (WFI)
6. Major emphasis on the economic, socio-economic and legal implications of test results, resulting in more testing and the requirement for more accurate testing, traceability and simplicity of understanding.
7. Better developed and more accurate and accountable on-line and field instrumentation.
8. More awareness in the scientific community of the need for secondary standards that have practical shelf lives, well defined measurement uncertainties, and are affordable and fit for purpose.
9. A greater proliferation of global and trans-national companies giving greater necessity for comparability of both time and place.
10. Increased activity in areas such as technology transfer, transfer of know-how including liaison between industry and universities leading to greater emphasis on standardisation of methodologies and comparability.

For these reasons and for Quality Control and validation purposes good quality standards including low-level conductivity standards are required. The criteria for the selection of such standards being:

- Accurately determined conductivity value
- Traceable to primary standards
- Matrix-matched to the sample (these are almost exclusively aqueous)
- Proven stability
- Readily available

Other elements that include health and safety pertaining to use, shipping and storage are also critical, as are considerations relating to toxicity, carcinogenicity and mutogenicity from a personal and environmental perspective.

In order to overcome the instability of low-level aqueous conductivity standards, caused by absorption of atmospheric carbon dioxide, a number of manufacturers offer conductivity standards containing organic solvents, e.g. propanol or glycerol[(5,6)]. These standards require a high degree of temperature control during use, due to their very high temperature coefficients of variation[(6,7)] and will also introduce matrix errors. It would be preferable to be able to use low-level, aqueous conductivity standards; however, a number of recent publications[(8,9)] have concluded that low-level conductivity standards with proven stability are not commercially available.

Reagecon have conducted a detailed stability study of their complete range of aqueous conductivity standards (from 1.3 to 500,000µS/cm). These standards are manufactured using an innovative process that is designed to counteract the effect of absorption of atmospheric carbon dioxide on the conductivity value of the standards.

However, carbon dioxide is not the only factor that has a deleterious effect on conductivity standards: the growth of micro-organisms, leaching of ions from the bottle, cap or other wetted parts of the container or from the manufacturing apparatus may also have a profound effect. As it to be expected, because of the lower ionic strength of low conductivity solutions, ions from any extraneous source will have a greater pro-rata effect on the conductivity of low level standards and therefore introduce greater error as a function of time. Solutions of Potassium Chloride form a suitable substrate for the growth of micro-organisms. However, because of the low isotonicity of low level standards, the work in our laboratory has shown that standards from 50µS down are less prone to contamination with values in the 50,000 – 200,000 µS region showing the greatest propensity for microbial growth. It is probable that such standards are of an ionic strength conducive to the growth of such organisms and that neither the cation or anion is toxic to at least certain types of bacteria[(14)]. It must also be borne in mind that prevention of any of the effects cited above must last over the lifetime of the product and the accuracy, uncertainty of measurement and shelf life are directly dependent and assigned on the basis of the results of all of these extraneous contaminants as a function of time. It must also be remembered that the effects of carbon dioxide emanate from 2 sources: diffusion through the wall of the container and from the headspace of the bottle, which increases as the liquid in the bottle is used up. Finally from the point of view of a working control it is an imperative that the temperature co-efficient and variation is as low as possible. This is because under normal laboratory working conditions there may be a temperature variation of up to 10°C in non-air conditioned laboratories. It is highly recommended that the temperature of sample and control be maintained at constant temperature (optimally at 25°C) but such conditions may not be warranted or possible from a "fitness for purpose" perspective. Under field conditions the variations or fluctuations in temperature are often substantially greater so a wide co-efficient of variation may lead to very erroneous results. Whilst such errors may be within the realms of acceptability for conductivity measurement it is vital that the co-efficient of the standard is as low as possible.

1.3 Features of Reagecon Standards

The introduction of the new technology for stabilising conductivity standards has achieved the following objectives:

1. Prevent shift in the conductivity value due to the effects of atmospheric carbon dioxide from either: the head space or through the container wall.
2. Prevent shift of value or spoilage of the standards due to fungal, bacterial or other microbial contamination or growth.
3. Keep the temperature co-efficient of variation per degree centigrade as low as possible.
4. Assign a practical and pragmatic shelf life to each standard that would render the range of products appropriate as secondary standards from a commercial perspective. In other words assign and apply a realistic curve of stability as a function of time to each product.
5. Assign an appropriate accuracy and measurement uncertainty to each standard conducive to the use of secondary standards and useable from a practical perspective.
6. Ensure that the matrix of the standard solvent is comparable or similar to water and that it exhibited the same electrolyte properties as water from an ionic interaction, viscosity, ionic strength, mobility and stability standpoint.
7. Ensure that the container would not have a deleterious effect on the standards from the perspective of leaching of ions into the standard, adsorption, or absorption of ions from the standard or that the container would be of a very high porosity that would allow greater gaseous exchange, particularly ingress of carbon dioxide or egress of carbon dioxide or other gases.

8. Ensure that the product would have minimal quantities of preservatives or other materials that might render the standards toxic, flammable, or irritant from a shipping, storage, user or environmental perspective.
9. Ensure the products were of a composition that meant that from manufacturing perspective the contained raw materials, manufacturing processes and/or testing processes that are practical, cost effective and affordable to all categories of users.
10. Ensure that the range of values produced span the requirements of the marketplace in terms of range and in particular that standards in the region of 1µS could be produced. Having studied the literature relating to the development and evolution of conductivity standards and factoring points 1 – 9 above into account, this proved to provide the greatest technical challenge.
11. If possible the products developed (particularly low conductivity standards) could be shipped and stored at ambient temperature as opposed to the constraints, costs and inconvenience of refrigerated temperature (2-8°C).

1.4 Summary of Experimental work

Gingerella and Jacanin[9][c] conducted stability studies on a number of manufacturers' low-level conductivity standards and found that their performance did not match the manufacturers' stability claims. These authors called for manufacturers of low-level conductivity standards to prove that the performance of their products complied with their published specifications and expiry dates and to revise their specifications (if necessary) or to remove their products from the market.

Reagecon responded and have conducted a detailed stability study of their complete range of aqueous conductivity standards (from 1.3 to 500,000µS/cm) as stated already. This paper details the findings of this study in abbreviated form for the low-level standards - 1.3 & 5µS/cm[d][10]. The results of this study address the concerns raised by Gingerella and Jacanin and show that Reagecon's conductivity standards comply with the selection criteria required for low-level conductivity standards. The study investigated the effect of the following factors on the stability of Reagecon's conductivity standards:

[c] Did not include Reagecon standards

[d] On the basis of extensive work carried out by Barron and Ashton we can demonstrate that if 1.3 µS/cm and 5µ/cm are stablised from the perspective of carbon dioxide interference then higher values will also be stable. For the purpose of conciseness the results of studies for 5µS/Cm and 1.3µS/Cm are presented here.

- Head-space in the bottle
- Storage temperature
- Bottle material

However in the interest of brevity, study details and results are substantially abbreviated in this paper and results and commentary pertaining to bottle material and storage temperature are excluded.

Reagecon's published specifications and expiry dates for their low-level conductivity standards are shown in Table 1.

Conductivity Standard value (µS/cm at 25 °C)	**Expiry Date (From Q.C. approval)**	**Specified Tolerance (µS/cm at 25 °C)**
5.00	6 months	4.95 – 5.05 (± 1%)
1.30	3 months	1.25 – 1.35

Table 1: Published Specifications and Expiry Dates of Reagecon's Conductivity Standards

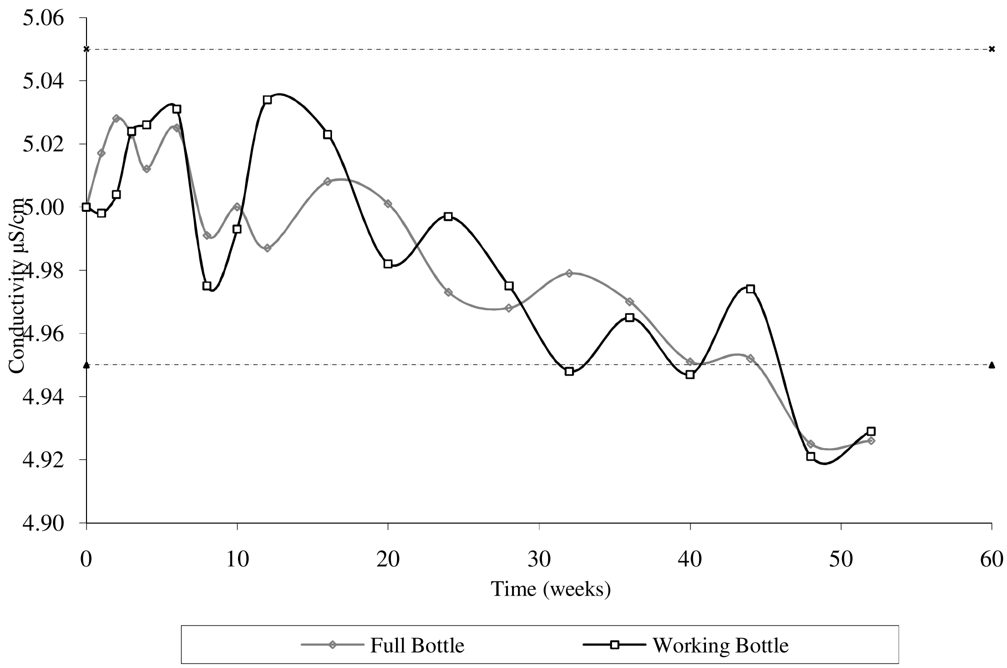
1.5 Simulated Working Conditions and Discussion - 5µS/cm samples

1.5.1 Stability of 5µ/cm Standards

Throughout the working life of a typical bottle of conductivity standard, aliquots are periodically removed from the bottle and then the bottle is re-capped and placed back into storage. It is important for the analyst to have confidence in the manufacturer's stated value for the standard until the solution is fully used or the stated expiry date is reached.

Graph 1 shows that for both working bottle samples and freshly opened bottle samples there is an initial rise in the measured conductivity value, followed by a steady drop in the measured conductivity value over the course of the stability study. The measured value of the working bottle samples falls outside the lower specification limit after 32 weeks, whilst the measured value of the fresh bottle samples falls outside the lower specification limit after 48 weeks.

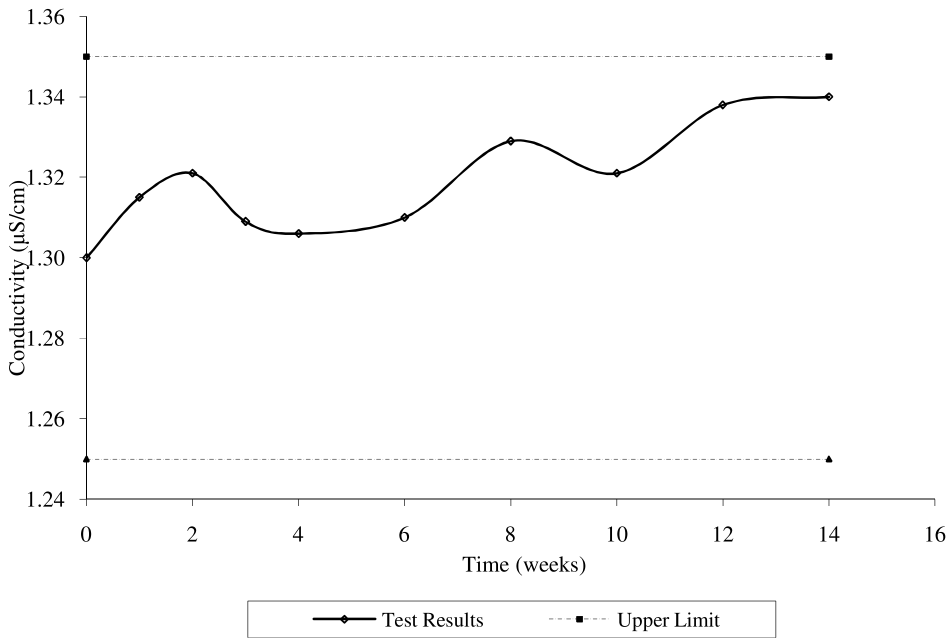
Reagecon assigns an expiry date of 6 months from the date of Quality Control approval for batches of their 5µS/cm conductivity standards. This period is less than the interval elapsed before either the working bottle or fresh bottle samples give a measured value outside of Reagecon's published specification limits.



Graph 1: 5µS/cm Samples at Room Temperature

1.5.2 Stability of 1.3µS/cm Samples

Reagecon's 1.3µS/cm conductivity standards are packaged in single-use bottles only. Consequently no investigation of working bottles was performed. Graph 2 demonstrates that Reagecon's 1.3µS/cm standard remains within the published specification limits of ±0.05µS/cm for the stated shelf life of 3 months.



Graph 2: 1.3µS/cm Samples Stored at Room Temperature

2.0 Conclusion

The results of the study described in this paper fully validate Reagecon's published shelf lives and specifications for their low-level conductivity standards.

The test results for the working, partially-full bottles of Reagecon's 5µS/cm conductivity standard demonstrate that analysts can have confidence in the integrity of this standard during its entire operational life. The test results for working bottles of Reagecon's 5µS/cm conductivity standard show a stability that exceeds the performance reported for freshly opened bottles of conductivity standards from alternative sources.

Similarly, test results for Reagecon's 1.3µS/cm conductivity standard validate the published specification and shelf life for this aqueous, low-level conductivity standard that is new to science.

Reagecon have answered the 'call to action' issued by Gingerella and Jacanin[9], whose analysis showed that other manufacturer's low-level conductivity standards failed to match their published specifications and shelf lives. Reagecon's innovative manufacturing process and careful selection of packaging material means that Reagecon are the only manufacturer that is able to offer demonstrably stable, aqueous, low-level conductivity standards. The availability of these low-level conductivity standards means that, for the first time, analysts have access to the standards required for validating their low conductivity measurements and analysts can have significantly increased confidence in their low conductivity test measurements.

3.0 Comparative Data[e]

Attribute	Control Company	Hamilton	Reagecon
Standard values up to 100µS/cm	1, 5, 10, 100µS/cm	1.3, 5. 15, 84, 100µS/cm	1.3, 5, 10, 20, 50, 84, 100µS/cm
Composition	1 –10: 30% isopropanol 100: 2% isopropanol	Glycerol in water (84 µS/cm also as aqueous)	All straight aqueous solutions
Specifications [i] (% of nominal value)	1µS/cm: 37% 5µS/cm: 8.8% 10µS/cm: 4.8% 100µS/cm: 1.0%	All 1%	1.3µS/cm: 3.9% All other values: 1%
Accreditation	ISO 9001, ISO 17025, ISO Guide 34	ISO 9001 only	ISO 9001, ISO 17025,
Testing	To ISO 17025	To ISO 17025 (performed by DFM - (Danish Metrology Institute)	To ISO 17025
COAs[ii]	With product only	On website	On website
Temperature coefficient	~3% (from NIST COA for similar product)	1.3µS/cm: 6.9% (no data for other values) [iv]	1.3µS/cm: 2.40% 100µS/cm: 1.96%
Expiry	No information provided	12 months for 1.3µS/cm 36 months for other non-aqueous standards 18 months for aqueous standards	3 months for 1.3µS/cm 6 months for 5 - 10µS/cm 12 months for 20 – 100µS/cm
Stability Data	None available	Journal published paper	Journal published paper
Packaging	100mls & 475mls plastic bottles	300mls glass bottles (500mls plastic for aqueous standards)	1.3µS/cm: 250mls plastic; other 500mls plastic
Hazards[iii]	1 - 10µS/cm: flammable	Irritant	none
Viscosity vs Water @25C[v]	1.4	~200	1
Standards over 100µS/cm	6 values: 1,000 – 200,000µS/cm	4 values: 147 – 12,880µS/cm	17 values: 147 – 500,000µS/cm

Table 2: Comparison of Low Conductivity Standards: Reagecon, Hamilton & Control Company

[e] Data prepared by Mr. C. Ashton, Reagecon Diagnostics Limited

1. Summary for Control Company:

i. The wide specification of Control Company's low conductivity standards makes them unsuitable for calibrating or verifying the response of conductivity instruments. Their website includes a convoluted description of the product specification – at best this is ambiguous and could be considered to be deliberately misleading. There is limited product information available on their website and no web-based COAs.

ii. Control Company's conductivity standards are flammable

iii. Making transport, storage, handling and disposal onerous and expensive.

2. Summary for Hamilton:

Hamilton provides a high quality product of tight specification, reliable QC and validated shelf-life. However, there are 2 major drawbacks with Hamilton's low conductivity standards:

iv. The very high temperature coefficient means that very tight temperature control and measurement are required for accurate conductivity measurement. It is virtually impossible to use Hamilton's standards and comply with the calibration requirements of the Pharmacopoeias that the cell constant must be known to 2%.

v. Very high viscosity – it is extremely onerous and time-consuming to remove all traces of these standards from the conductivity cell. Any trace of standard left on the cell will cause carry-over errors, so these standards reduce user confidence in their subsequent sample measurements.

3. Summary for Reagecon:

Reagecon's conductivity standards have tight specification, reliable QC and validated shelf-life. Their low temperature coefficient and aqueous composition allow for practical, accurate calibration and verification of conductivity instruments. They provide the only viable means of complying with Pharmacopoeial requirements.