Harmonization of Conductivity Tests for Pharmaceutical Waters[*]

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Abstract

The chemistry tests to verify of the quality of bulk Pharmaceutical Waters underwent substantial changes with the implementation of USP 23 in 1996. These qualitative tests were replaced with modern, quantitative, instrument-based tests such as conductivity and total organic carbon (TOC). The acceptance of these changes was not without its problems, but the resulting changes have improved Pharmaceutical Water quality control. Subsequently, the European Pharmacopeia implemented their versions of conductivity and TOC tests for Pharmaceutical Waters.

The conversion to these instrument-based tests represented a significant step towards unifying the tests for these EP and USP waters. The USP TOC monograph (<643>) is substantially identical to its operation and implementation in the EP (2.2.44). Interestingly, the less complicated and more technologically robust method of conductivity greatly differs between the USP and EP. The reasons for these differences are based on different application strategies. The similarities in these strategies are discussed. However, the practices espoused in the EP standard possess some technical faults or uncertainties which require reconsideration based on the science behind the water chemistry and conductivity.

Introduction

Chemical tests prior to USP 23

Before the implementation of USP 23, the water chemistry tests for bulk USP Purified Water (PW) and Water for Injection (WFI) consisted of analysis for heavy metals, five specific species (carbon dioxide, ammonia, chloride, calcium, and sulfate), oxidizable carbon, endotoxins, and microbiological activity. The tests for the five specific ions were "wet chemistry" tests. Generally, they require procuring and storing a sample, treating the sample with a reagent, and then making an observation. For example, the test for chloride is to treat the sample with a requisite amount of $AgNO_3$, and then examine the sample for a precipitate. However, upon the initial mixing of the reagent and water sample, a cloudiness in the sample may appear initially and then redissolve. But at what point does the lab technician decide that the cloudiness remains and the sample has failed? Or that the precipitate dissolved and the sample is acceptable?

A related example of an ambiguous test is the oxidizable substances test. The water sample is treated with permanganate and heat, and the sample has failed if the pink color disappears, resulting from complete consumption of the oxidizing permanganate ion. A passing result is achieved by the presence of pink remaining in the sample. The nature of the test requires an

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absorption spectrophotometer, not an uncalibrated eye that may be susceptible to biases such as room lighting or color perception.

The ability (or inability!) to observe microprecipitates and distinguish them from dust and other ambient particulates results in the potential for operator bias. Similarly, the presence or absence of a pink appearance requires interpretation. Furthermore, these types of tests result in a "pass" or "fail" status and they offer no information regarding the degree of success or failure. The USP chemical tests for PW and WFI, prior to USP 23, are comprised of these types of bias-laden methods for other ions.

Rationale for the Selection of Conductivity

Nearly a decade ago, it was formally recognized[1] that chemistry tests for USP PW and WFI had outlived their usefulness, and better tests were available. The Pharmaceutical Research and Manufacturers of America (PhRMA, formerly the PMA) and its expert Water Quality Committee had proposed to the United States Pharmacopeia a significant series of changes to the chemistry tests for these waters, based on the following premises. First, there was nothing wrong with the quality of water being produced, or the technologies used to produce the water. Therefore, there was no intent to modify the tests to improve the overall water quality. Second, though the existing tests dated back to the mid-1800's, it was not the age of the tests that were questioned. It was the fact that the proposed tests 1) were more quantitative and reliable, 2) eliminated or reduced operator bias, and 3) were currently operating in every pharmaceutical system.

If we focus on the following five chemistry tests that were required for USP PW and WFI – carbon dioxide, chloride, calcium, sulfate, and ammonia – a common bond among them is that each material is ionic** when present in water. Therefore, each material is conductive in water. This physical property allows them to be detected by conductivity analyzers at <0.001 mg/L (1 mg/L = 1 ppm) concentrations in high purity water because of the low background conductivity of pure water.

Furthermore, the use of conductivity as a QC and diagnostic tool by pharmaceutical facilities and their water systems engineers was common. Virtually every pharmaceutical water production system, from the smallest laboratory system to the largest industrial system, has a conductivity system in place to monitor the in-line water quality. Other than a home-built water system, a conductivity quality measurement is a standard feature on any ion-exchange, RO, EDI, or distillation purification unit. Therefore, the common use of conductivity and the detection limits of conductivity for these five chemical species made it a viable choice to implement as a replacement for the chemical tests.

Goals of the Efforts

Throughout the development and comment period from 1991 to 1996, there were concurrent PhRMA symposia and private communications. The goals of the proposed changes were unchanged throughout the process. They were :

** CO_2 (and NH_3) are neutral, but its reaction with water to form the HCO_3^- and H^+ (and NH_4^+ and OH^-) make them conductive.

- maintain or improve the existing water quality control
- improve the reliability of the testing
- simplify the testing (using modern instrumentation)
- reduce the number of tests
- make allowances for in-line testing

While there was no concerted effort to improve the water quality, there would be an improvement in water quality control because the inherent properties of the proposed measurement method, conductivity, could offer that when used to its fullest potential. The next goal, increasing reliability, could be achieved if issues such as operator bias and sample-handling could be reduced. Any efforts to lower testing costs must not impact quality.

The crucial element was the acknowledgement that in-line testing (measurements of water quality inside the process pipe) was a feature that could be exploited for its many benefits. For example, the cost of daily sample handling (labor, cleaning, storage) and the possibility of contamination could be eliminated. This goal did not enforce in-line testing. It only permitted it to take advantage of the conductivity measurements that were already being made.

Basic test philosophy

It was widely recognized that all water systems varied considerably in production capacity, system complexity, water quality, and control systems. To maintain flexibility, the conductivity test eventually evolved into a "3-stage" test plan to allow for 1) in-line testing and 2) the innocuous impurities such as CO_2 which directly impact off-line testing. The considerations were the following :

- Permit in-line or off-line testing.
- Set the maximum allowable conductivity to detect the maximum allowable quantity of the ion which produces the lowest conductivity. The maximum allowable quantity is based on conversion of the USP XXII test methods to analytically determined detection limits.
- For off-line tests, allow for innocuous contamination that results from normal exposure to CO_2 in the air (HCO_3^- and H^+).
- Eliminate the variations of temperature-compensation methods.

The benefit of in-line testing was to allow those operators to make use of their existing in-line conductivity instrumentation. The benefit of off-line testing was to allow those operators who were unable to make (or unfamiliar with making) in-line conductivity measurements. Furthermore, some facilities send out water samples to contract labs, so some contingency for these needs must be considered.

Current USP <645> Conductivity Test

The final details of the "3-stage" test plan and the determination evolved over several years and several iterations of testing, modeling, and discussions. The following summarizes some of the subtleties of the test method and the computational strategy.

Original conductivity limit

The conductivity limit was originally chosen to be 1.3 μS/cm at 25°C. This complete derivation of this value is provided elsewhere[1], and is briefly reviewed here. The concentration of the chloride ion is determined from the chemical test. If the product of $[Ag^+]$ and $[Cl^-]$ exceeds the solubility product, K_{sp}, of AgCl, then a precipitate would form and the water sample would fail this chloride test. From the test procedure, one determines that $[Cl^-] = 1.33 \times 10^{-5}$ mol/L (or 0.47 ppm) at the solubility limit. We know that there is H^+ and OH^- ions present resulting from the autodissociation of water. The concentration of each ion is determined according to

$$K_w = [H^+][OH^-] = 1.01 \times 10^{-14} \text{ at } 25°C \qquad \text{eq 1}$$

There is an interaction with the ambient impurities[2], CO_2. Based on a minimum of 300 ppm CO_2 in air[3], and the known solubility of CO_2 in water[4], the amount of resulting H_2CO_3 and HCO_3^- is determined according to[4]:

$$K_{a1} = \frac{[H^+][HCO_3^-]}{[CO_2]_{aq}} = 4.45 \times 10^{-7} \text{ at } 25°C \qquad \text{eq 2}$$

The second acid dissociation of H_2CO_3 is negligible for this discussion. The resulting charge balance equation is

$$[H^+] + [Na^+] = [OH^-] + [HCO_3^-] + [Cl^-] \qquad \text{eq 3}$$

The inclusion of a common ion such as Na^+ is required to complete the charge balance.

At various pH values, the concentration of each ion can be determined from eq 1-3 and the definition of pH. This results in the ion concentrations shown in Table 1 at 25°C as a function of pH. Eq 1 and 2 are temperature dependent, and this dependence is well-known from the literature[4] and standard textbooks. K_{sp} is not pH dependent.

Table 1. Concentration of Ions at 25°C at the Limiting Chloride Concentration

pH	$[H^+]$ (mol/L)	$[OH^-]$ (mol/L)	$[HCO_3^-]$ (mol/L)	$[Cl^-]$ (mol/L)	$[Na^+]$ (mol/L)
5.0	1.00E-05	1.01E-09	4.42E-07	1.33E-05	3.70E-06
5.1	7.94E-06	1.27E-09	5.57E-07	1.33E-05	5.87E-06
5.2	6.31E-06	1.60E-09	7.01E-07	1.33E-05	7.65E-06
5.3	5.01E-06	2.02E-09	8.82E-07	1.33E-05	9.13E-06
5.4	3.98E-06	2.54E-09	1.11E-06	1.33E-05	1.04E-05
5.5	3.16E-06	3.19E-09	1.40E-06	1.33E-05	1.15E-05
5.6	2.51E-06	4.02E-09	1.76E-06	1.33E-05	1.25E-05
5.7	2.00E-06	5.06E-09	2.22E-06	1.33E-05	1.35E-05
5.8	1.58E-06	6.37E-09	2.79E-06	1.33E-05	1.45E-05
5.9	1.26E-06	8.02E-09	3.51E-06	1.33E-05	1.55E-05
6.0	1.00E-06	1.01E-08	4.42E-06	1.33E-05	1.67E-05
6.1	7.94E-07	1.27E-08	5.57E-06	1.33E-05	1.80E-05
6.2	6.31E-07	1.60E-08	7.01E-06	1.33E-05	1.97E-05
6.3	5.01E-07	2.02E-08	8.82E-06	1.33E-05	2.16E-05
6.4	3.98E-07	2.54E-08	1.11E-05	1.33E-05	2.40E-05
6.5	3.16E-07	3.19E-08	1.40E-05	1.33E-05	2.70E-05
6.6	2.51E-07	4.02E-08	1.76E-05	1.33E-05	3.07E-05
6.7	2.00E-07	5.06E-08	2.22E-05	1.33E-05	3.53E-05
6.8	1.58E-07	6.37E-08	2.79E-05	1.33E-05	4.11E-05
6.9	1.26E-07	8.02E-08	3.51E-05	1.33E-05	4.83E-05
7.0	1.00E-07	1.01E-07	4.42E-05	1.33E-05	5.75E-05

1.33×10^{-5} mole/L of chloride ion is 0.47 ppm.

The conductivity of a solution is determined from

$$k\,(\mathrm{S/cm}) = 10^{-3} \sum_{i}^{\substack{\text{all} \\ \text{ions}}} \lambda_i^\circ C_i \qquad\qquad \text{eq 4}$$

For this case, the following equation is applied.

$$k\,(S/cm) = \frac{\lambda_{H^+}[H^+] + \lambda_{OH^-}[OH^-] + \lambda_{HCO_3^-}[HCO_3^-] + \lambda_{CO_3^{2-}}[CO_3^{2-}] + \lambda_{Na^+}[Na^+] + \lambda_{Cl^-}[Cl^-]}{1000} \qquad \text{eq 5}$$

where $[X_i]$ is the concentration of ion i (in moles/L) and λ_i is the specific conductance of ion i at infinite dilution (in S-cm²/mole)[4]. For the 5 species present in this "solution of ions at the theoretical chloride limit", the conductivity at 25°C can be determined from the ion concentration and eq 5. The results are listed in Table 2.

Table 2. Conductivity of Ions at 25°C at the Limiting Chloride Concentration

pH	[H+] (μS/cm)	[OH-] (μS/cm)	Sum of [H$^+$] & [OH$^-$] (μS/cm)	[HCO$_3$$^-$] (μS/cm)	[Cl$^-$] (μS/cm)	[Na$^+$] (μS/cm)	Total (μS/cm)
5.0	3.49	0.00	3.49	***0.02***	***1.01***	***0.19***	4.71
5.1	2.77	0.00	2.77	0.02	1.01	0.29	4.11
5.2	2.20	0.00	2.20	0.03	1.01	0.38	3.63
5.3	1.75	0.00	1.75	0.04	1.01	0.46	3.26
5.4	1.39	0.00	1.39	0.05	1.01	0.52	2.97
5.5	1.10	0.00	1.10	0.06	1.01	0.58	2.76
5.6	0.88	0.00	0.88	0.08	1.01	0.63	2.60
5.7	0.70	0.00	0.70	0.10	1.01	0.68	2.48
5.8	0.55	0.00	0.55	0.12	1.01	0.73	2.42
5.9	0.44	0.00	*0.44*	*0.16*	*1.01*	*0.78*	2.39
6.0	0.35	0.00	0.35	0.20	1.01	0.84	2.40
6.1	0.28	0.00	0.28	0.25	1.01	0.90	2.44
6.2	0.22	0.00	0.22	0.31	1.01	0.99	2.53
6.3	0.18	0.00	0.18	0.39	1.01	1.08	2.67
6.4	0.14	0.01	0.14	0.49	1.01	1.20	2.85
6.5	0.11	0.01	0.12	0.62	1.01	1.35	3.10
6.6	0.09	0.01	0.10	0.78	1.01	1.54	3.43
6.7	0.07	0.01	0.08	0.99	1.01	1.77	3.85
6.8	0.06	0.01	0.07	1.24	1.01	2.06	4.38
6.9	0.04	0.02	0.06	1.56	1.01	2.42	5.06
7.0	0.03	0.02	***0.06***	1.97	1.01	2.88	5.92

The sum of the four **bold, italicized** values is 1.27 μS/cm.
The sum of the four *italicized* values at 5.9 pH is 2.39 μS/cm.
All values have been rounded to the nearest 0.01 μS/cm.

The minimum conductivity value for each ion (the sum of [H+] and [OH-] was treated collectively) was summed and the result was 1.27 μS/cm. This is represented by highlighted values in Table 2.

This strategy and model were repeated for the other four ions (carbon dioxide, ammonia, calcium, and sulfate) for which chemical tests were required. In each case, the specific ion conductivities and chemical balance equations were slightly different to account for different chemical equilibria, counterions, and specific conductivities, but the philosophy was the same. The conductivity was calculated based on known physical and chemical properties of each ion at its concentration limit based on the chemical tests. In each case, the conductivity was greater than 1.27 μS/cm, the closest being 1.29 μS/cm for the ammonia model. This resulted in the initial publicized value of 1.3 μS/cm at 25°C for an on-line measurement[1].

For off-line measurements, it was understood that there would be a greater intrusion of CO_2 into the water sample, and that intrusion would adversely impact (increase) the conductivity. In fairness to those that would be testing off-line, there would be an allowance for that increase based on the minimum amount of CO_2 in air, and the conductivity increase that would result. The conductivity limit for off-line testing would then be the minimum of the sum of all ions at any pH from 5 to 7. This is indicated in Table 2 by the italicized values at 5.9 pH. The conductivity limit for off-line testing was initially determined to be 2.4 µS/cm at 25°C[1].

Initial Validation of the Method
The WQC proceeded to determine if the proposed test limits were reasonable and valid. They procured conductivity instrumentation from numerous suppliers that met a basic minimum criteria, and then set out to use this instrumentation to demonstrate that today's pharmaceutical waters systems could meet this test limit on-line and off-line.

The initial results of the testing were quite unexpected. Basically, when each instrument was operating in "temperature-compensated" mode, the results from the different instruments did not agree with each other. Yet, when the temperature-compensation feature was disabled in each meter, there was uniformity in the results between the varying instruments. In private discussions with us, the WQC learned about the harsh realities and subtleties of conductivity temperature compensation.

Temperature compensation requires a separate discussion that can be found elsewhere[5-6]. Briefly, temperature compensation is the method of adjusting the signal output to the value that the signal would be at a reference temperature. In the case of conductivity, the non-linear temperature-dependence on the conductivity requires complex and very accurate algorithms to accurately adjust the raw measurement at any temperature to the compensated value if the fluid were at 25°C. The purpose of this is two-fold. First, to allow the end-user to distinguish between temperature changes and water purity changes. The second is to provide a universal reference point to benchmark and compare system performances without having to be concerned with temperature effects. These compensation algorithms vary from supplier to supplier, depending upon the instrument capability and knowledge of high purity water. Regardless of the reasons for the differences, the fact was that there were substantial differences among instruments that could not be resolved.

When the effect of compensation was removed and there was general agreement between instruments, the philosophy of the conductivity measurement required re-examination. Eventually, the WQC asked us to extend the existing modeling that was done. The idea was to have a "temperature-dependent" conductivity limit and eliminate the temperature compensation effect. This would allow the use of on-line instrumentation to monitor water purity for water systems whose temperature was not at 25°C. We repeated the calculations from 0-100°C at 5°C intervals for the chloride model. This would result in series of increasing conductivity limit values as a function of temperature, and a single value of 2.4 µS/cm at 25°C for off-line testing.

Chloride-Ammonia Model

After the calculations were repeated for the chloride model, the conductivity limits were re-determined as a function of temperature. It was presumed that since the chloride model provided the minimum conductivity at 25°C, it would provide the minimum conductivity at all temperatures and pH. We challenged this assumption and it led to the following series of changes[7].

Only the ammonia-chemistry, with its low test limit of 0.3 ppm, would offer a challenge to the chloride model to provide the lowest conductivity at its test limit. So the ammonia model was re-calculated as a function of temperature. The ionic components of the ammonia model were different than the chloride model since the chemical equilibria and charge balance would be different, but the philosophy was the same. For the ammonia model, sodium and chloride ions were used to maintain electro-neutrality. Tables 3 and 4 provide the concentration and conductivities of the ammonia model at 25°C. With this available information, similar tables were prepared at 5°C intervals from 0-100°C for the ammonia and chloride models.

Table 3. Concentration of Ions at 25°C at the Limiting Ammonia Concentration

pH	$[H^+]$ (mol/L)	$[OH^-]$ (mol/L)	$[HCO_3^-]$ (mol/L)	$[Cl^-]$ (mol/L)	$[Na^+]$ (mol/L)	$[NH4^+]$ (mol/L)	$[NH_3]_{aq}$ (mol/L)	$[NH_4^+]$ (ppm)
5.0	1.00E-05	1.01E-09	4.42E-07	2.62E-05	0.00E+00	1.66E-05	9.47E-10	3.00E-01
5.1	7.94E-06	1.27E-09	5.57E-07	2.40E-05	0.00E+00	1.66E-05	1.19E-09	3.00E-01
5.2	6.31E-06	1.60E-09	7.01E-07	2.22E-05	0.00E+00	1.66E-05	1.50E-09	3.00E-01
5.3	5.01E-06	2.02E-09	8.82E-07	2.08E-05	0.00E+00	1.66E-05	1.89E-09	3.00E-01
5.4	3.98E-06	2.54E-09	1.11E-06	1.95E-05	0.00E+00	1.66E-05	2.38E-09	3.00E-01
5.5	3.16E-06	3.19E-09	1.40E-06	1.84E-05	0.00E+00	1.66E-05	2.99E-09	3.00E-01
5.6	2.51E-06	4.02E-09	1.76E-06	1.74E-05	0.00E+00	1.66E-05	3.77E-09	3.00E-01
5.7	2.00E-06	5.06E-09	2.22E-06	1.64E-05	0.00E+00	1.66E-05	4.74E-09	3.00E-01
5.8	1.58E-06	6.37E-09	2.79E-06	1.54E-05	0.00E+00	1.66E-05	5.97E-09	3.00E-01
5.9	1.26E-06	8.02E-09	3.51E-06	1.44E-05	0.00E+00	1.66E-05	7.52E-09	3.00E-01
6.0	1.00E-06	1.01E-08	4.42E-06	1.32E-05	0.00E+00	1.66E-05	9.46E-09	3.00E-01
6.1	7.94E-07	1.27E-08	5.57E-06	1.18E-05	0.00E+00	1.66E-05	1.19E-08	3.00E-01
6.2	6.31E-07	1.60E-08	7.01E-06	1.02E-05	0.00E+00	1.66E-05	1.50E-08	3.00E-01
6.3	5.01E-07	2.02E-08	8.82E-06	8.27E-06	0.00E+00	1.66E-05	1.89E-08	3.00E-01
6.4	3.98E-07	2.54E-08	1.11E-05	5.87E-06	0.00E+00	1.66E-05	2.38E-08	3.00E-01
6.5	3.16E-07	3.19E-08	1.40E-05	2.90E-06	0.00E+00	1.66E-05	2.99E-08	2.99E-01
6.6	2.51E-07	4.02E-08	1.76E-05	0.00E+00	8.01E-07	1.66E-05	3.76E-08	2.99E-01
6.7	2.00E-07	5.06E-08	2.22E-05	0.00E+00	5.43E-06	1.66E-05	4.73E-08	2.99E-01
6.8	1.58E-07	6.37E-08	2.79E-05	0.00E+00	1.12E-05	1.66E-05	5.95E-08	2.99E-01
6.9	1.26E-07	8.02E-08	3.51E-05	0.00E+00	1.85E-05	1.66E-05	7.49E-08	2.99E-01
7.0	1.00E-07	1.01E-07	4.42E-05	0.00E+00	2.77E-05	1.65E-05	9.42E-08	2.98E-01

Table 4. Conductivity of Ions at 25°C at the Limiting Ammonia Concentration

pH	[H+] (µS/cm)	[OH-] (µS/cm)	Sum of [H$^+$] & [OH$^-$] (µS/cm)	[HCO$_3^-$] (µS/cm)	[Cl$^-$] (µS/cm)	[Na$^+$] (µS/cm)	[NH$_4^+$] (µS/cm)	Total (µS/cm)
5.0	3.49	0.00	3.49	*0.02*	2.00	*0.00*	*1.22*	6.73
5.1	2.77	0.00	2.77	0.02	1.83	0.00	1.22	5.85
5.2	2.20	0.00	2.20	0.03	1.70	0.00	1.22	5.15
5.3	1.75	0.00	1.75	0.04	1.58	0.00	1.22	4.60
5.4	1.39	0.00	1.39	0.05	1.49	0.00	1.22	4.15
5.5	1.10	0.00	1.10	0.06	1.40	0.00	1.22	3.79
5.6	0.88	0.00	0.88	0.08	1.33	0.00	1.22	3.50
5.7	0.70	0.00	0.70	0.10	1.25	0.00	1.22	3.27
5.8	0.55	0.00	0.55	0.12	1.18	0.00	1.22	3.08
5.9	0.44	0.00	0.44	0.16	1.10	0.00	1.22	2.92
6.0	0.35	0.00	0.35	0.20	1.01	0.00	1.22	2.78
6.1	0.28	0.00	0.28	0.25	0.90	0.00	1.22	2.65
6.2	0.22	0.00	0.22	0.31	0.78	0.00	1.22	2.54
6.3	0.18	0.00	0.18	0.39	0.63	0.00	1.22	2.42
6.4	0.14	0.01	0.14	0.49	0.45	0.00	1.22	2.31
6.5	0.11	0.01	0.12	0.62	0.22	0.00	1.22	2.18
6.6	0.09	0.01	0.10	0.78	0.00	0.04	1.22	2.14
6.7	0.07	0.01	0.08	0.99	0.00	0.27	1.22	2.56
6.8	0.06	0.01	0.07	1.24	0.00	0.56	1.22	3.09
6.9	0.04	0.02	0.06	1.56	0.00	0.93	1.22	3.77
7.0	0.03	0.02	*0.06*	1.97	*0.00*	1.39	1.22	4.63

The sum of the four **bold, italicized** values is 1.29 µS/cm.

The sum of the five *italicized* values at 6.6 pH is 2.14 µS/cm.

All values have been rounded to the nearest 0.01 µS/cm.
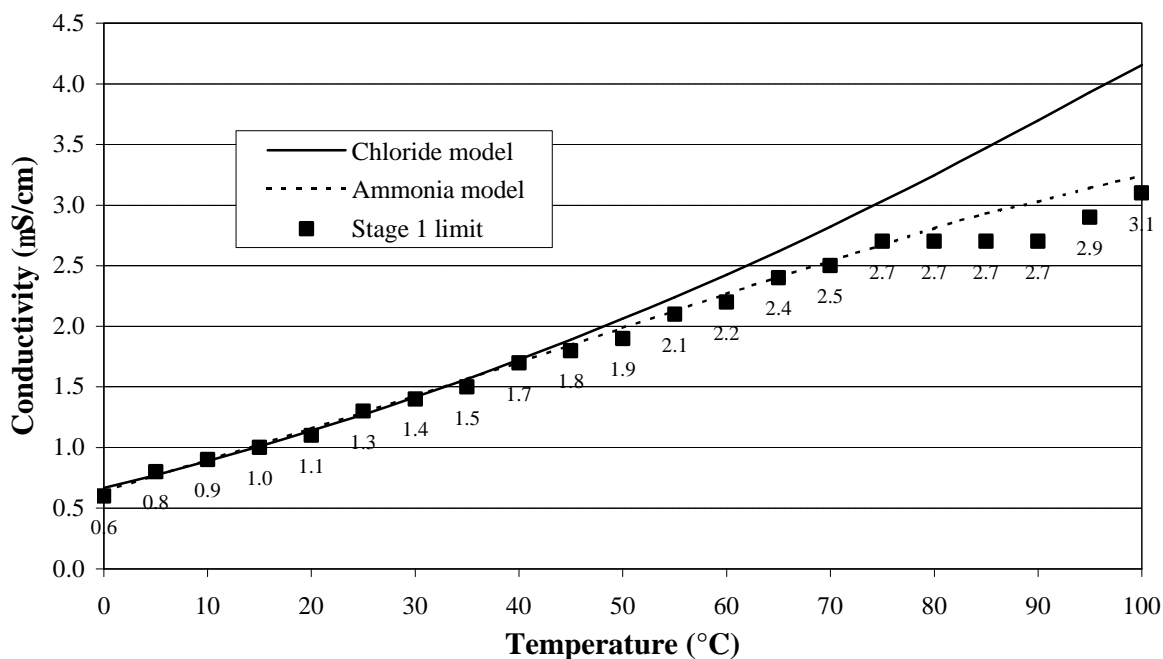
Results for Stage 1 Testing

When these calculations were completed, a table of conductivity vs. temperature for the chloride and ammonia models was generated (see Table 5). At temperatures up to 45°C, the two models provide nearly identical conductivities with the chloride model providing the minimum conductivity at and near 25°C. But above 45°C, the chloride conductivity model increases faster than the ammonia model, owing to numerous factors. As a result, the ammonia model results in the lowest (or limiting) conductivity under these conditions.

The results of the conductivity modeling and its temperature dependence of the chloride and ammonia models are displayed in Table 5 and Figure 1. The Stage 1 on-line test is based on the resulting combined "chloride-ammonia" model which provides the basis for the temperature-dependent conductivity limit. The small discrepancies between the model and the actual value have never been resolved, but they are minor in nature do not warrant further comment.

Table 5. Limiting Conductivity for Each Model and Stage 1 Conductivity Limit

Temp. (°C)	Chloride Model Cond. (µS/cm)	Ammonia Model Cond. (µS/cm)	<645> Stage 1 Limit (µS/cm)	Temp. (°C)	Chloride Model Cond. (µS/cm)	Ammonia Model Cond. (µS/cm)	<645> Stage 1 Limit (µS/cm)
0	0.66	0.64	0.6	55	2.24	2.13	2.1
5	0.77	0.77	0.8	60	2.43	2.27	2.2
10	0.89	0.90	0.9	65	2.62	2.41	2.4
15	1.01	1.03	1.0	70	2.82	2.54	2.5
20	1.14	1.16	1.1	75	3.03	2.67	2.7
25	1.27	1.29	1.3	80	3.24	2.81	2.7
30	1.42	1.43	1.4	85	3.47	2.93	2.7
35	1.57	1.56	1.5	90	3.70	3.03	2.7
40	1.73	1.70	1.7	95	3.93	3.14	2.9
45	1.89	1.85	1.8	100	4.16	3.24	3.1
50	2.06	1.99	1.9				

Figure 1. Conductivity vs. Temperature for Each Model and Stage 1 Conductivity Limits


Results for Stage 2/3 Testing

When we determined that the ammonia model resulted in the limiting conductivity at higher temperatures, this caused us to go back and recheck the calculations as a function of pH. The chloride ion model resulted in a minimum conductivity of 2.39 µS/cm at 5.9 pH and 25°C based on the minimum total conductivity as a function of pH. When the calculation was repeated (see

Table 4), we found that the philosophy used to calculate the Stage 2 limit results in a new lower conductivity, 2.14 μS/cm for the ammonia model. This would later be rounded conservatively to 2.1 μS/cm, the eventual Stage 2 test limit[8].

When the impact of varying amount of CO_2 was considered, and its impact on pH and conductivity, some flexibility in the test methods was needed. Since water (equilibrated with air) was required to possess a 5.0-7.0 pH, it made sense to develop the model as a function of pH. This led to the Stage 3 test limits that are pH dependent. In this process of this development, we also learned that the chloride model results in the limiting conductivity at the low pH, but the ammonia model results in limiting conductivity at pH>6.2. By varying the pH, subtle changes in the chemistries result, and the subsequent Stage 3 conductivity limit is a hybrid of each model. The results of each model and the Stage 3 <645> limit are shown here[8].

Table 6. Limiting Conductivity for Each Model and Stage 3 Conductivity Limit

pH (pH)	Chloride Model Cond. (μS/cm)	Ammonia Model Cond. (μS/cm)	<645> Stage 3 Limit (μS/cm)	pH (pH)	Chloride Model Cond. (μS/cm)	Ammonia Model Cond. (μS/cm)	<645> Stage 3 Limit (μS/cm)
5.0	4.71	6.72	4.7	6.1	2.44	2.65	2.4
5.1	4.11	5.85	4.1	6.2	2.53	2.54	2.5
5.2	3.63	5.15	3.6	6.3	2.67	2.42	2.4
5.3	3.26	4.60	3.3	6.4	2.85	2.31	2.3
5.4	2.97	4.15	3.0	6.5	3.10	2.18	2.2
5.5	2.76	3.79	2.8	6.6	3.43	2.14	2.1
5.6	2.60	3.50	2.6	6.7	3.85	2.56	2.6
5.7	2.48	3.27	2.5	6.8	4.38	3.09	3.1
5.8	2.42	3.08	2.4	6.9	5.06	3.77	3.8
5.9	2.39	2.92	2.4	7.0	5.92	4.63	4.6
6.0	2.40	2.78	2.4				

Figure 2. Conductivity vs. pH for Each Model and Stage 3 Conductivity Limits
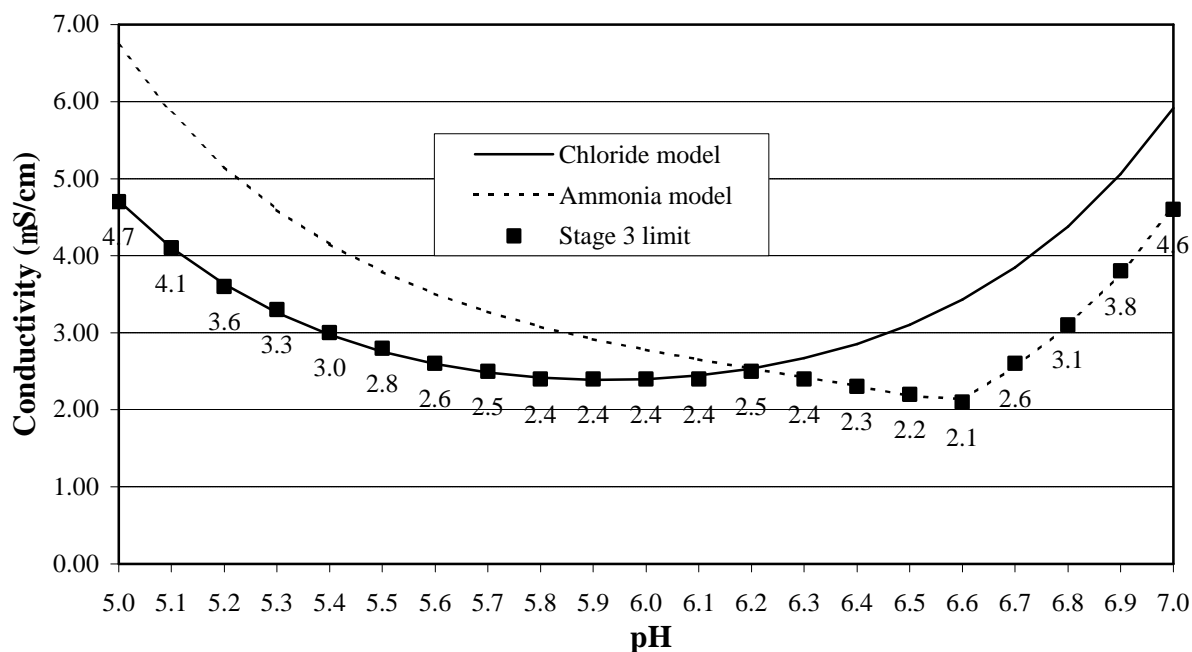
Other Requirements of <645>
A few other requirements of <645> are briefly mentioned here.

- The meter reports uncompensated conductivity or uncompensated resistivity.
- The display resolution is 0.1 µS/cm or better.
- The meter reads accurately to ±0.1 µS/cm when a 0.1% precision resistor replaces the sensor (to calibrate/verify the meter).
- The sensor cell constant is calibrated/verified to ±2% in solutions of known conductivity.

The latter three items insure that a certain minimum level of instrument quality is provided. These criteria are based on available commercial instrumentation from numerous manufacturers and from the basic minimum requirements to accurately make the desired conductivity measurements.

Summary of <645>
After a few years of implementation of conductivity testing, the impact to the pharmaceutical facility has been minor, after a normal adjustment period. The keys to the success of the implementation were the flexibility in the testing (on- and off-line), its allowance for harmless contamination from CO_2, and its variable limits based on definable chemical and physical properties of water and the ions which required chemical testing previously.

The decision to replace antiquated chemical tests with conductivity for USP waters was simple because conductivity has been a reliable and quantitative method that can be used on- and off-line. The strategy to use non-temperature-compensated measurements and the "chloride-ammonia" model to determine limits were controversial initially. The method and limits were

based on experimental data, instrument practicality, and a consistent concept to account for all chemical tests, temperatures, and on-line/off-line measurements.

Transformation of the Chemical Model from USP to EP

When the strategy to replace chemical tests with conductivity was proposed to the EP, the conductivity test was embraced. However, the model was applied differently than in the USP. The discussion shall focus on these differences and the controversial sections of <645> and 2.2.38. The brief list is presented here, and the detailed discussion of each point follows.

- The limits in 2.2.38 have a dependence on the type of water, while the USP does not distinguish between PW and WFI for the conductivity testing. EP's modification of the strategy is innovative because it promotes the concept that WFI should be purer than Purified Water.
- Why is the test for nitrates still required? It is a redundant test.
- There is no provision (apparently) for on-line conductivity.
- Is the conductivity measurement compensated or non-temperature-compensated?
- The concentrations and values in Table 2.2.38.1 are incorrect.
- There a no meter calibration or performance requirements to insure a minimum level of quality.
- The conductivity limit for WFI is dangerously low for off-line measurements.
- The EP includes bulk and packaged waters, the USP only bulk.
- The USP and EP have harmonized on the use of a conductivity method. Can the details of the conductivity method be extended?

Application of the Chemical Model

The USP "chloride-ammonia" model was extended to the EP for use. It was applied for a different set of EP chemical tests, and eventually it was determined that the limiting (lowest) conductivity is achieved based on the minimum nitrate and ammonia ion concentration at 0.2 ppm. Since these ions have been historically prevalent in European water supplies, and since these ions also have had chemistry tests required to meet EP PW and WFI requirements, the EP application is entirely consistent with the USP application.

Upon application of the chemistries associated with these nitrogenated ions, at table similar to Tables 1 and 2 can be prepared based on these chemistries. When this was completed, the resulting limiting conductivity was determined to be 1.1 µS/cm for the nitrate/ammonia model at the specific concentration at 25°C. This value is lower than the equivalent USP limit (1.3 µS/cm) due to the lower limiting concentration and slightly different chemistries.

Using the same model for the USP Stage 2/3 test, except introducing ammonia/nitrate at 0.2 ppm, results in a conductivity limit at 25°C of 1.1 to 4.3 µS/cm, depending on the pH. Again, the values are lower than the USP model, but the underlying reasons are based on different chemistries.

Determination of Conductivity Limits for EP PW and WFI

With the result of the model in hand, the EP elected to apply its results in a substantially different way than the USP model. They selected the 1.1 µS/cm value as the WFI limit and the 4.3 µS/cm value as the PW limit. To our knowledge, the basis for this selection has never been presented, but that is not relevant. However, we can infer that the reason to have different conductivity limits for PW and WFI is because of the inherent higher quality required of WFI.

The fact that the USP and EP applied the same philosophy and model, but interpreted the results differently is not debated in this paper. Clearly, each had its reasons. The tendency of the US audience was to question why the EP would interpret the model in a different way than the USP, but the fact is neither standards agency is beholden to the other. Furthermore, since there has always been a distinction of microbiological test limits for PW and WFI, there is something very sound in the practice to require an lower conductivity (ionic) limit for WFI.

Furthermore, the USP has two tables of conductivity values that users must be familiar for the production of PW or WFI. One is a the temperature-dependent conductivity limits for Stage 1 on-line testing, and the other is the pH-dependent conductivity limits for Stage 3 off-line testing. The EP limits require knowledge of only two numbers and not two tables of numbers. There is a high degree of simplicity in the EP philosophy.

With the acceptance of a simpler set of conductivity limits in the EP water requirements, there also comes a certain amount of confusion and incompleteness that was not realized during the discussion process. These points are not trivial, as they have been raised not just by persons with unique conductivity backgrounds, but the concerns have been raised by pharmaceutical water producers.

Temperature Compensation and Measurements at 20°C

Throughout the EP water monographs and the Conductivity test, there is no mention of temperature compensation for the measurements. There are some inferences, but there is no clear communication. Upon discussion at a Parenteral Society Symposium, there was certainly no clear consensus whether the 2.2.38 authors intended to use compensated measurements or not. It appears from the monographs that temperature-compensation for conductivity measurements are not understood.

First, the 2.2.38 Conductivity test requires measurements at 20°C. This leads to at least two, possibly more, flaws in the test method. First, if the test needs to be done at 20°C, this virtually precludes the ability to execute in-line testing. Many PW and most WFI systems produce water at temperature much greater than 20°C. In order for the test to be executed at 20°C, precise heat exchangers would be required to reduce the temperature of the water line for subsequent measurement at 20°C. This would be inefficient and costly. It would also conflict with the desire to keep temperatures high to control the microbiological activity.

If we presume that that 2.2.38 does not intend for temperature compensation to be allowed, then this should be stated clearly. Prior to the implementation of USP 23 <645>, the use on

non-temperature compensated conductivity measurements was non-existent. All conductivity systems come standard with options for temperature compensation, just like pH analyzers.

If 2.2.38 does intend for temperature compensation to be allowed, then we are faced with another dilemma. All laboratory fluid measurements (laboratory and on-line process analyzers) such as pH and conductivity are referenced to 25°C. Each instrument offers single or multiple temperature compensation algorithms. Furthermore, virtually all conductivity analyzers (laboratory and on-line process analyzers) offer linear compensation to 25°C. Linear compensation is a means of adjustment of the signal according to

$$k_{25} = \left(\frac{k_{\mathrm{T}}}{1 + a(\mathrm{T} - 25)} \right) \qquad \text{eq 6}$$

where κ_{25} is the compensated conductivity, κ_{T} is uncompensated conductivity at temperature T (in °C), and α is the decimal temperature coefficient (%/°C). For example, a typical salt solution has a 2%/°C response, or $\alpha=0.02$. If it is the intention to require compensation to 20°C, then the test method does not consider the availability of instrumentation.

Perhaps it is intended for the user to execute the linear compensation using eq 6, and not automatically by the meter. Again, the lack of clear communication makes one try to interpret 2.2.38, and perhaps incorrectly. Furthermore, in 2.2.44 Total Organic Carbon, the test method specifies TOC water to be 1.0 µS/cm at 25°C. Why would there be a requirement to test this water at 25°C, but the water for conductivity testing is measured at the unusual temperature of 20°C?

On-line vs. Off-Line Measurements
It is possible that the intent of the test method is to make all measurements off-line and in the laboratory. There is nothing scientifically wrong with this, except that the greatest practical benefits of conductivity measurements are achieved by on-line measurements. Making these measurements off-line is defeating much of its benefit and makes no sense for a technically sound and robust technology such as conductivity. Yet, there is specific mention in the TOC (2.2.44) test that on-line measurements are permissible if the test method and apparatus is validated. There is no mention of the allowance (or denial) of on-line conductivity measurements. From this lack of detail, one may interpret that on-line conductivity measurements are not allowed. Another person may interpret that conductivity measurements are allowed since on-line conductivity is commonplace in pharmaceutical water systems. This reader cannot confidently interpret the standard. In comparison to <645> where the topic of temperature compensation is written explicitly and clearly, there is no clear indication in 2.2.38.

Meter Calibration and Performance Requirements
The WQC and the USP included certain quality requirements to guide users in the appropriate operation and calibration of instrumentation. The most glaring omission is the lack of a meter accuracy requirement. There is no calibration or accuracy or display resolution requirement for the meter, and thus no control over minimum quality standards.

Sensor Calibration

From the perspective of a user to meet USP requirements, the issues described to this point are possibly minor, depending on their interpretation. It is not the technical aspects, but the ambiguities in the description of the test method that cause uncertainty to this point. In fact, insofar as the requirements for sensor calibration are concerned, 2.2.38 is very clear about the test limits. Sensor accuracy has been allowed to be ±5%, where as the USP requires ±2%. Since it is common for most pharmaceutical water systems to produce water that is 2-10× better (lower in conductivity) than is required, the differences in required accuracy (2% or 5%) is very minor. In fact, it has been suggested to the USP by some US pharmaceutical end users to open this test limit up to ±5%. The USP test does not require that specific reference (standard) solutions to be used, only that the sensors be tested in the appropriate solutions. So while the <645> does not overregulate, it does not offer guidance and puts the burden on the user.

In contrast, 2.2.38 takes the ambiguity out and describes specific standard solutions to use. However, several of the calibration standard solutions described in Table 2.2.38.1 are in error. Although it is not referenced, the conductivity solutions described in this table at 18°C and 25°C are derived from the ASTM D1125 Test Method[9], and references contained therein. The original references are based on conductivity data taken at 18°C (127.54 µS/cm) and 25°C (146.93 µS/cm). Then, to determine the conductivity at 20°C, the conductivity data at 18°C and 25°C was interpolated to 20°C, arriving at the value of 133.08 µS/cm. This value was rounded to 133 µS/cm. This estimation by interpolation is valid based on the properties of conductive solutions over a small temperature range. The validity of this solution is not in question.

However, from the description of the solutions listed in Table 2.2.38.1 to prepare the 1330 µS/cm and 26.6 µS/cm conductivity standards, it is evident there was a presumption that the conductivity is directly proportional to the concentration. This is not that case, as there are always negative deviations from linearity, even at concentration less than 0.01 mol/L. The negative deviations are on the order of 2-10% per decade depending in the chemical species and concentration.

Table 7 lists the solution concentration, conductivity at 25°C, and equivalent ASTM solutions. The 133.0 µS/cm standard (at 20°C) suggested by the EP is identical to Solution D in ASTM D1125. The 1330 µS/cm standard is based on a 10× more concentrated solution and obviously presumes a 10× more conductive solution. But the equivalent ASTM solution (Solution D) would be 1274.3 µS/cm at 20°C.

Table 7. Concentration and Conductivity Data from ASTM and 2.2.38

Table 2.2.38.1 EP method	KCl (g/L)	at 0°C (uS/cm)	at 18°C (uS/cm)	at 25°C (uS/cm)	at 20°C (uS/cm)
est. 10-fold dilution	0.7455				**1330.0**
Y	0.0746				**133.0**
est. 5-fold dilution	0.0149				**26.6**
ASTM method					
Sol C	0.7440	773.6	1220.5	1408.8	**1274.3**
Sol D	0.0744	77.69	127.54	146.93	**133.08**
est. 5-fold dilution	0.0149	15.54	25.51	29.39	**26.62**

Taken from Table 2.2.38.1

In addition, the 26.6 µS/cm is based on a 5× dilution of the 133 µS/cm solution and the presumption that the conductivity is precisely linear with concentration. However, there are no ASTM or any other recognized standard solutions at this concentration. The conductivity of this 5× diluted solution would be ~30-31 µS/cm, which differs from the proposed standard by ~15%. This type of linear extrapolation is inadequate and not based on properties of conductive solutions, and will result in cell constant errors of 15% or more.

It is recognized that conductivity standard preparation below 100 µS/cm is difficult due to contamination errors and susceptibility to air. That is precisely the reason that the ASTM has not adopted lower conductivity standards, to date. Nonetheless, it is desirable to have lower conductivity standards that are in the proximity of the actual operating measurement range. Some solutions to remedy this problem are the use of high purity water as a standard[6,10] and an alternative validation method[11].

Summary

Is this truly "harmonization"? Of course not, but significant steps have been taken to move in the same direction. The most critical technical weaknesses of the 2.2.38 Conductivity method are the lack of clarity regarding temperature compensation, the requirement to measure at 20°C, the lack of allowance for on-line measurements, and the incorrect solution conductivity for the 26.6 µS/cm and 1330 µS/cm standards. There must be some means to permit on-line conductivity measurements if TOC measurements are permitted to be in-line. The most commonplace TOC analyzers for on-line process measurement are based on conductivity measurements.

The EP philosophy to require separate limits for PW and WFI is very clever and innovative and requires further discussion by the EP and USP. But the basic premise of conductivity measurement methods is to eliminate the chemical testing. Why is the nitrate test still required in the EP water monographs? If there is acceptance that the conductivity test is equal to or better, why have redundant testing?

References

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2. T.S. Light, B. Kingman, A.C. Bevilacqua, "The Conductivity of Low Concentrations of CO_2 Dissolved in Ultrapure Water from 0-100°C", *209th American Chemical Society National Meeting*, Anaheim, CA, April 2-6, 1995.

3. The concentration of 300 ppm CO_2 in pristine air that was used in these models was actually low. The value at that time was ~330 ppm, and it is now nearly 350 ppm. However, the models are not very sensitive to the CO_2 concentration in this range, and would have a very small impact on the ultimate conductivity.

4. Information such as the solubility of CO_2 in H_2O, the dissociation constant of H_2CO_3, and specific ion conductances can be found in standard reference texts such as the Handbook of Chemistry and Physics, *CRC Press*.

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