Article appeared in International Laboratory News August 2000 edition

Conductivity measurement on pure water according to the recommendations of the USP Pharmacopoeia USP24-NF19

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Pharmaceutical laboratories working in the US market are obliged to respect the regulations set down by the US Pharmacopoeia. The 5th supplement of USP24-NF19 lays down the rules for checking the quality of pure or fully deionised water used for the production of injection products. These rules are not particularly easy to implement and the expertise of a manufacturer of analytical instruments like Radiometer Analytical is a crucial aid.

The conductivity of water provides information on its chemical composition. It is therefore logical that USP24-NF19 makes this the main parameter to measure. This recommendation is very demanding in terms of the quality of the apparatus to be used (conductivity meter, conductivity cell and standard solution). In some conditions, the pH value of the water can be taken.

What the recommendation says
The conductivity of water is directly linked to the concentration of the ions and their mobility. The conductivity depends on the value of the pH, on the temperature of measurement and on the amount of CO_2 which has been dissolved in the water to form ions. The conductivity due to these factors is “intrinsic conductivity”.

The conductivity is also affected by the concentration of ions already present in the water such as chloride, sodium and ammonium. This contribution to the conductivity is “extraneous conductivity”.

Step 1: **Measurement of conductivity (intrinsic and extraneous) and the temperature** of the water. The measured values are compared to values laid down by USP *(see table no.1*). There is no temperature correction; the conductivity is read at the temperature of measurement. The use of a circulation type conductivity cell is highly recommended to avoid any increase in conductivity due to ambient CO_2. For instance, at a temperature of 20°C, the conductivity value measured has to be below or equal to the corresponding conductivity value given in the table, in this case 1.1 µS/cm. If the conductivity of the water is below this limit, the quality of the pure water is acceptable and the water is suitable for use in pharmaceutical products. If the conductivity is greater than 1.1 µS/cm, additional tests have to be performed in order to determine if this too high conductivity is due to intrinsic or extraneous factors.

Step 2**: Shows the effect of CO_2 (intrinsic factor).** This is achieved by performing a conductivity measurement at 25 ±1°C on a sample of water, which is vigorously stirred (the use of a thermostated vessel to maintain the temperature constant is recommended). The variation of the conductivity is followed and the measurement is taken when the variation is below 0.1 µS/cm for 5 minutes. According to this step of the USP, the conductivity value measured must be less than 2.1 µS/cm. If the conductivity is higher than this value, proceed with Step 3.

Step 3: **The combined effects of CO_2 and pH are studied** in this final step. Measuring pH in low ionic strength solutions is extremely difficult. To solve this instability problem, add a saturated KCl solution (0.3 ml for 100 ml of sample) to the pure water sample used in step 2. The temperature stays constant at 25 ±1°C, and pH is measured with a resolution of 0.1 pH unit. The pH value obtained must be between 5.0 and 7.0. For each intermediate pH value, there is a corresponding limit in conductivity (*see table no. 2*). For instance, water with a pH equal to 5.8, must have a conductivity below 2.4 µS/cm. If the conductivity value is higher, then the quality of this water is not sufficient and it cannot be used to manufacture pharmaceutical products.

Table no. 1: *Values from USP24 – NF19, 5th Supplement, (645)* "Temperature and conductivity requirements (for non temperature-compensated conductivity measurements only)"

Temperature (°C)	Conductivity (µS/cm)
0	0.6
5	0.8
10	0.9
15	1.0
20	1.1
25	1.3
30	1.4
35	1.5
40	1.7
45	1.8
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7
95	2.9
100	3.1

Table no. 2: *Values from USP24 – NF19, 5th Supplement, (645)* «pH and conductivity requirements (for atmosphere and temperature equilibrated samples only)"

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

Which instruments to use

Steps 1 and 2:
Steps 1 and 2 require high-quality instruments. The instrument must be calibrated and possess a valid calibration certificate drawn up by the manufacturer. Radiometer Analytical offers the following equipment to perform the first two steps of the USP requirement: the CDM230 Conductivity Meter, CDC511T Conductivity Cell (flow-through type cell using new 4-pole technology and fitted with a built-in temperature sensor, see photo) and the KCl 0.01D certified conductivity standard solution.

The recommendation specifies that the conductivity meter used must have 0.1 µS/cm as minimum resolution on the lower range and the meter uncertainty (excluding the cell uncertainty) must be ±0.1 µS/cm. **The CDM230 advanced conductivity meter** from Radiometer Analytical easily meets these requirements. A dedicated range for low conductivity is available from 0.001 to 4.000 µS/cm with a resolution of 1 nS/cm. A calibration certificate can be established by the Metrology department of Radiometer Analytical to prove the fitness of the instrument for the application.

USP requirements regarding the conductivity cell are more complicated as they concern the value of the constant. *(Remember the crucial role of this factor because it is systematically used to calculate the conductivity, see Appendix 1 « Theory»). From the* USP24-NF19 norm, the value of the cell constant must be known to within ±2%. During the determination of the constant, the two main factors are the conductivity cell itself and the standard solution. Which cell and which standard used to reach the uncertainty level required?

The uncertainty of the constant value results from the contribution of uncertainties from all variables that are used in the determination of that constant. The prime source of uncertainty is the expanded uncertainty of the conductivity standard solution. The maximum uncertainty due to all the other variables is estimated as 1%. Therefore, to be able to determine a cell constant to within ±2%, the expanded uncertainty of the standard solution has to be less than ±1%. In other words, the standard solution to be used will have a conductivity value higher than that of the water to be measured because it will be a waste of time to look for a standard of low conductivity with an expanded uncertainty lower than ±1%.
NIST[(1)] recently performed a study on this subject and the results are convincing [(2)]. For instance, for a 5 µS/cm standard solution, the expanded uncertainty obtained is ±4.7% provided that the temperature stays constant at ±0.002°C. For a 15 µS/cm standard solution, the expanded uncertainty already reaches ±1.6%. Obviously, it is not possible today to have standard solutions of low conductivity with an expanded uncertainty lower than ±1%.
It is possible, however, to find a standard solution which satisfies this criteria from 1000 µS/cm. Radiometer Analytical produces a **KCl 0.01D conductivity standard** which has a certified conductivity value of 1408 µS/cm at 25°C with a tolerance of ±0.5% specified using an expanded uncertainty (k=2). This standard is fully traceable to NIST Certified Reference Material and is connected to the international conductivity scale (demal scale), as recommended by OIML(*3). Radiometer Analytical has received accreditation by the calibration department of Cofrac(*4) for Chemistry and Reference Materials (n°2.1418), for the calibration of reference materials in conductivity and pH. By using this standard solution, you can take advantage of a full and recognised traceability chain and calculated uncertainties all described on the certificates provided.

Because of the choice of this standard solution, the conductivity cell to be used has to be designed with 4-pole technology. Only this type of cell is able to guarantee a perfect linearity over several decades thanks to the non polarisation of the electrodes. In other words, only a 4-pole cell can be used to perform a calibration around 1400 µS/cm and to measure conductivity on ultra pure water around 0.1 µS/cm.
To briefly explain this concept, a current (I) is applied to the 2 outer electrodes and a voltage (U) is measured between the 2 inner electrodes which are linked to high

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impedance inputs of the amplifier. Because there is no current in the high impedance input circuit, there is no polarisation phenomenon on the electrodes used for the measurement.
The **CDC511T Conductivity Cell** features this new technology in the form of 4 platinum rings. This circulation type cell is specially designed to be ready to use to measure conductivity protected from the air. The sample passes through the cell in a continuous flow. For Step 2 the 'circulation piece' of the cell is removed and replaced by a new accessory better adapted for this measurement. A calibration certificate which guarantees the value of the constant with an expanded uncertainty lower than 1% (k=2) can be drawn up on request by the Metrology Department of Radiometer Analytical.

<u>Step no. 3:</u>
The demand regarding the specifications of the instrument to be used in Step 3 is standard. A pH has to be measured with a 0.1 resolution. This can easily be performed with the **PHM210 Standard pH Meter** from Radiometer Analytical. A verification certificate established by the manufacturer will confirm the conformity of the instrument to its specifications. With the pHC2085-8 Combined pH Electrode, which has a built-in temperature sensor, pH and temperature are measured at the same time in order to ensure that the temperature was 25 ±1°C as required by USP. Calibration of this pH measuring chain is performed using certified standard pH solutions, IUPAC Series pH4.005 and pH7.000, which are delivered with a Cofrac verification certificate and a conformity and traceability certificate draw up following ISO Guide 31.

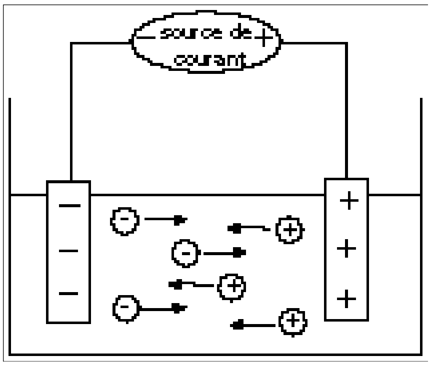
Radiometer Analytical's offer covers all the points of the USP24-NF19 recommendation. A practical application note is also available. Many pharmaceutical laboratories have already purchased this system to help them follow USP24-NF19. This equipment can also be used for industrial applications by comparing calibrations.

Photo: CDC511T, *4-pole conductivity cell with built-in temperature sensor.*

Circulation type cell for measurements protected from the air.

Appendix 1: Theory

Conductivity is the ability of a solution to pass an electric current between two electrodes. The current is carried by ions; therefore, the conductivity increases with the number of ions present in solution and their mobility. A solution will resist current flow if a small amount of ions is present. This solution is resistant, the resistivity is the opposite of the conductivity.



Scheme: Ionic migration in solution

To measure conductivity, a voltage (U) is applied to the two platinum electrodes of the cell, and the resulting current (I) is measured. In practice, in order to reduce the polarisation of the electrodes, the conductivity meter applies an alternative voltage at a dedicated frequency.
By using Ohm's law (U = R x I), the resistance of the solution (R) can be calculated.
R = U/I
From that, the conductance (G) is determined using the formulae:
G = 1/R then G= I/U

The conductivity of a solution (Kappa) is calculated on the basis of the conductance (G), and is given by the expression:

Kappa = G K with*

Kappa = conductivity (S/cm)
G = conductance (S)
K = Cell constant value (cm^{-1})

The cell constant (K) is based on the geometry of the cell and can, in theory, be calculated from the dimensions of the electrodes (plates or rings) using the following formulae:

K = l/A, with

l = distance between the electrodes (cm)
A = area of the electrodes (cm^2)
In practice, it is difficult to measure the real area of the electrodes precisely. This is why standard solutions of known conductivity are used to calibrate the cell.

- [1] NIST = National Institute of Standards and Technology, USA
- [3] OIML = Organisation Internationale de Métrologie Légale. See Recommendation no. 56.
- [4] Cofrac = Comité Français d'Accréditation (French Accreditation Scheme)

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