

Matching Fluids

Matching Fluid	Parts of Cobaltous Chloride CS	Parts of Ferric Chloride CS	Parts of Cupric Sulfate CS	Parts of Water
A	0.1	0.4	0.1	4.4
B	0.3	0.9	0.3	3.5
C	0.1	0.6	0.1	4.2
D	0.3	0.6	0.4	3.7
E	0.4	1.2	0.3	3.1
F	0.3	1.2	0.0	3.5
G	0.5	1.2	0.2	3.1
H	0.2	1.5	0.0	3.3
I	0.4	2.2	0.1	2.3
J	0.4	3.5	0.1	1.0
K	0.5	4.5	0.0	0.0
L	0.8	3.8	0.1	0.3
M	0.1	2.0	0.1	2.8
N	0.0	4.9	0.1	0.0
O	0.1	4.8	0.1	0.0
P	0.2	0.4	0.1	4.3
Q	0.2	0.3	0.1	4.4
R	0.3	0.4	0.2	4.1
S	0.2	0.1	0.0	4.7
T	0.5	0.5	0.4	3.6

## (641) COMPLETENESS OF SOLUTION

Place the quantity of the substance specified in the individual monograph in a meticulously cleansed, glass-stoppered, 10-mL glass cylinder approximately 13 mm × 125 mm in size. Using the solvent that is specified in the monograph or on the label of the product, fill the cylinder almost to the constriction at the neck. Shake gently to effect solution: the solution is not less clear than an equal volume of the same solvent contained in a similar vessel and examined similarly.

## (643) TOTAL ORGANIC CARBON

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, and from biofilm growing in the system. TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system. A TOC measurement is not a replacement test for endotoxin or microbiological control. While there can be a qualitative relationship between a food source (TOC) and microbiological activity, there is no direct numerical correlation.

A number of acceptable methods exist for analyzing TOC. This chapter does not endorse, limit, or prevent any tech-

nologies from being used, but this chapter provides guidance on how to qualify these analytical technologies for use as well as guidance on how to interpret instrument results for use as a limit test.

Apparatus commonly used to determine TOC in water for pharmaceutical use have in common the objective of oxidizing the organic molecules in the water to produce carbon dioxide followed by the measurement of the amount of carbon dioxide produced. Then the amount of CO<sub>2</sub> produced is determined and used to calculate the organic carbon concentration in the water.

All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO<sub>2</sub> and bicarbonate, and the CO<sub>2</sub> generated from the oxidation of organic molecules in the sample. The discrimination may be accomplished either by determining the inorganic carbon and subtracting it from the total carbon (total carbon is the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. While purging may entrain organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

**Apparatus Requirements**—This test method is performed either as an on-line test or as an off-line laboratory test using a calibrated instrument. The suitability of the apparatus must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg of carbon per L (0.05 ppm of carbon) or lower.

When testing water for quality control purposes, ensure that the instrument and its data are under appropriate control and that the sampling approaches and locations of both on-line and off-line measurements are representative of the quality of the water used. The nature of the water production, distribution, and use should be considered when selecting either on-line or off-line measurement.

**USP Reference Standards (11)**—USP 1,4-Benzoquinone RS. USP Sucrose RS.

**Reagent Water**—Use water having a TOC level of not more than 0.10 mg per L. [NOTE—A conductivity requirement may be necessary to ensure method reliability.]

**Container Preparation**—Organic contamination of containers results in higher TOC values. Therefore, use labware and containers that have been scrupulously cleaned of organic residues. Any method that is effective in removing organic matter can be used (see *Cleaning Glass Apparatus* (1051)). Use *Reagent Water* for the final rinse.

**Standard Solution**—Unless otherwise directed in the individual monograph, dissolve in the *Reagent Water* an accurately weighed quantity of USP Sucrose RS, to obtain a solution having a concentration of 1.19 mg of sucrose per L (0.50 mg of carbon per L).

**System Suitability Solution**—Dissolve in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 0.75 mg per L (0.50 mg of carbon per liter).

**Reagent Water Control**—Use a suitable quantity of *Reagent Water* obtained at the same time as that used in the preparation of the *Standard Solution* and the *System Suitability Solution*.

**Water Sample**—Obtain an on-line or off-line sample that suitably reflects the quality of water used.

**Other Control Solutions**—Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument, if necessary.

**System Suitability**—Test the *Reagent Water Control* in the apparatus, and record the response,  $r_w$ . Repeat the test using the *Standard Solution*, and record the response,  $r_s$ . Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water*

Control response from the response of the *Standard Solution*. The theoretical limit of 0.50 mg of carbon per L is equal to the corrected *Standard Solution* response,  $r_s - r_w$ . Test the *System Suitability Solution* in the apparatus, and record the response,  $r_{ss}$ . Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*,  $r_{ss} - r_w$ . Calculate the percent Response Efficiency for the *System Suitability Solution* by the formula:

$$\% \text{ Response Efficiency} = 100[(r_{ss} - r_w)/(r_s - r_w)]$$

where  $r_s$  is the instrument response to the *Standard Solution*;  $r_{ss}$  is the instrument response to the *System Suitability Solution*; and  $r_w$  is the instrument response to the *Reagent Water Control*. The system is suitable if the percent Response Efficiency is not less than 85% and not more than 115%.

**Procedure**—Perform the test on the *Water Sample*, and record the response,  $r_u$ . The *Water Sample* meets the requirements if  $r_u$  is not more than the limit response,  $r_s - r_w$ . This method can be performed using on-line or off-line instrumentation that meets the *Apparatus Requirements*.

## (645) WATER CONDUCTIVITY

Electrical conductivity in water is a measure of the ion-facilitated electron flow through it. Water molecules dissociate into ions as a function of pH and temperature and result in a very predictable conductivity. Some gases, most notably carbon dioxide, readily dissolve in water and interact to form ions, which predictably affect conductivity as well as pH. For the purpose of this discussion, these ions and their resulting conductivity can be considered intrinsic to the water.

Water conductivity is also affected by the presence of extraneous ions. The extraneous ions used in modeling the conductivity specifications described below are the chloride and sodium ions. The conductivity of the ubiquitous chloride ion (at the theoretical endpoint concentration of 0.47 ppm when it was a required attribute test in *USP XXII* and earlier revisions) and the ammonium ion (at the limit of 0.3 ppm) represent a major portion of the allowed water impurity level. A balancing quantity of cations, such as sodium ions, is included in this allowed impurity level to maintain electroneutrality. Extraneous ions such as these may have significant impact on the water's chemical purity and suitability for use in pharmaceutical applications. The procedure in the section *Bulk Water* is specified for measuring the conductivity of waters such as Purified Water, Water for Injection, Water for Hemodialysis, and the condensate of Pure Steam. The procedure in the section *Sterile Water* is specified for measuring the conductivity of waters such as Sterile Purified Water, Sterile Water for Injection, Sterile Water for Inhalation, and Sterile Water for Irrigation.

Online conductivity testing provides real-time measurements and opportunities for real-time process control, decision, and intervention. Precaution should be taken while collecting water samples for off-line conductivity measurements. The sample may be affected by the sampling method, the sampling container, and environmental factors such as ambient carbon dioxide concentration and organic vapors.

## INSTRUMENT SPECIFICATIONS AND OPERATING PARAMETERS

Water conductivity must be measured accurately using calibrated instrumentation. The conductivity cell constant, a factor that represents the geometrical properties of the conductivity sensor, must be known within  $\pm 2\%$ . The cell constant can be verified directly by using a solution of known or traceable conductivity, or indirectly by comparing the instrument reading taken with the conductivity sensor in question to readings from a conductivity sensor of known or traceable cell constant.

Meter calibration is accomplished by replacing the conductivity sensor with NIST (or equivalent local national authority) -traceable precision resistors (accurate to  $\pm 0.1\%$  of the stated value) or an equivalently accurate adjustable resistance device, such as a Wheatstone Bridge, to give a predicted instrument response. Each scale on the meter may require separate calibration prior to use. The frequency of recalibration is a function of instrument design, degree of use, etc. However, because some multiple-scale instruments have a single calibration adjustment, recalibration may be required between each use of a different scale. Excluding the conductivity sensor cell constant accuracy, the instrument accuracy must be  $\pm 0.1 \mu\text{S/cm}$ .

In order to increase the measurement accuracy on the conductivity ranges used, which can be large, and to ensure a complete equipment calibration, it is suggested that periodic verification of the entire equipment be performed. This could be done by comparing the conductivity/resistivity values displayed by the measuring equipment with those of an external calibrated conductivity-measuring device. The two nontemperature-compensated conductivity or resistivity values must be equivalent to within  $\pm 20\%$  of each other, or at a difference that is acceptable on the basis of product water criticality and/or the water conductivity ranges in which the measurements are taken. The two conductivity sensors should be positioned close enough together to measure the same water sample in the same environmental conditions.

In addition to the verification method performed in nontemperature-compensated mode, a similar verification performed in temperature-compensated mode could be performed to ensure an appropriate accuracy of the equipment when such a mode is used for trending or other purposes.

Because temperature has a substantial impact on conductivity readings of specimens at high and low temperatures, many instruments automatically correct the actual reading to display the value that theoretically would be observed at the nominal temperature of  $25^\circ$ . This is typically done using a temperature sensor embedded in the conductivity sensor and an algorithm in the instrument's circuitry. This temperature compensation algorithm may not be accurate. Conductivity values used in this method are nontemperature-compensated measurements. Temperature measurement is required for the performance of the *Stage 1* test. It may be made using the temperature sensor embedded in the conductivity cell sensor. An external temperature sensor positioned near the conductivity sensor is also acceptable. Accuracy of the temperature measurement must be  $\pm 2^\circ$ .

The procedures below shall be performed using instrumentation that has been calibrated, has conductivity sensor cell constants that have been accurately determined, and has temperature compensation function that has been disabled. For both online and offline measurements, the suitability of instrumentation for quality control testing is also dependent on the sampling location(s) in the water system. The selected sampling instrument location(s) must reflect the quality of the water used.

## BULK WATER

The procedure and test limits in this section are intended for Purified Water, Water for Injection, Water for Hemodial-