⟨643⟩ TOTAL ORGANIC CARBON

Change to read:

INTRODUCTION

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, from biofilm growing in the system, and from the packaging of sterile and nonsterile waters. TOC also can 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. Although 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 technologies from being used, but this chapter provides guidance on how to qualify these analytical technologies ▲as well as▲ (USP 1-May-2021) how to interpret instrument results for use as a limit test.

Apparatuses 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 carbon dioxide 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 carbon dioxide and bicarbonate, and the carbon dioxide 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 (▲▲ (USP 1-May-2021) the sum of organic carbon and inorganic carbon), or by purging inorganic carbon from the sample before oxidation. Although purging may entrain ▲volatile▲ (USP 1-May-2021) organic molecules, such purgeable organic carbon is present in negligible quantities in water for pharmaceutical use.

PROCEDURES

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1. Bulk Water

The following sections apply to tests for bulk *Purified Water*, *Water for Injection*, *Water for Hemodialysis*, and the condensate of *Pure Steam*.

1.1▲ Instrumentation▲ (USP 1-May-2021) 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 ▲instrument▲ (USP 1-May-2021) must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.05 mg/L (0.05 ppm) or lower of carbon.

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 ▲▲ (USP 1-May-2021) water ▲purification process,▲ (USP 1-May-2021) distribution, and use should be considered when selecting either on-line or off-line measurement.

1.2 Reagent water: Use water with a TOC level of NMT 0.10 mg/L. [NOTE—A conductivity requirement may be necessary to ensure method reliability.]

1.3 Container preparation: Organic contamination of ▲labware and sample▲ (USP 1-May-2021) 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* (section 1.2) for the final rinse.

1.4 System suitability solution: Dissolve an accurately weighed quantity of USP 1,4-Benzoquinone RS in *Reagent water* (section 1.2) to obtain a solution with a concentration of 0.75 mg/L (0.50 mg/L of carbon).

1.5 Standard solution: Unless otherwise directed in the individual monograph, dissolve an accurately weighed quantity of USP Sucrose RS in the *Reagent water* (section 1.2) to obtain a solution with a concentration of 1.19 mg/L of sucrose (0.50 mg/L of carbon).

1.6 Reagent water control: Use a suitable quantity of *Reagent water* (section 1.2) obtained at the same time as those used in the preparations of the *Standard solution* (section 1.5) and the *System suitability solution* (section 1.4).

1.7 Water sample: Obtain an on-line or off-line sample that suitably reflects the quality of water used.

1.8 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.

▲1.9 Limit response: Measure the TOC of the *Reagent water control* (section 1.6) in the instrument, and record the response (r_w). Also measure the TOC of the *Standard solution* (section 1.5) in the instrument, and record the response (r_S). Calculate the corrected *Standard solution* response, which is also the *Limit response* (r_L), for the contribution from the *Reagent water* (section 1.2), by subtracting the *Reagent water control* response from the *Standard solution* response:

$$r_L = r_S - r_W$$

r_S = instrument response to the *Standard solution* (section 1.5)
r_W = instrument response to the *Reagent water control* (section 1.6)

The *Limit response* (r_L) of 0.50 mg/L of carbon will be equal to this corrected *Standard solution* response.▲ (USP 1-May-2021)

1.10 System suitability: ▲ Measure the TOC of the *System suitability solution* (section 1.4) in the instrument, and record the response (r_{SS}). Calculate the corrected *System suitability solution* response (r_C) by subtracting the *Reagent water control* response from the *System suitability solution* response:

$$r_C = r_{SS} - r_W$$

r_{SS} = instrument response to the *System suitability solution* (section 1.4)
r_W = instrument response to the *Reagent water control* (section 1.6)

Calculate the percent response efficiency (r_E):

$$r_E = 100 \times [(r_C / r_L)$$

r_C = corrected instrument response to the *System suitability solution* (section 1.4)
r_L = corrected instrument response to the *Standard solution* (section 1.5) (also known as the *Limit response*)▲ (USP 1-May-2021)

The ▲TOC measuring▲ (USP 1-May-2021) system is suitable if the percent response efficiency (r_E) is NLT 85% and NMT 115%. ▲The suitability of the instrument must be periodically demonstrated.▲ (USP 1-May-2021)

1.11 Procedure: ▲Measure the TOC of▲ (USP 1-May-2021) the *Water sample* (section 1.7) and record the response (r_U). The *Water sample* meets the requirements if r_U is NMT ▲r_L.▲ (USP 1-May-2021)This method can be performed using on-line or off-line instrumentation that meets the ▲*Instrumentation*▲ (USP 1-May-2021) *requirements* (section 1.1).

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2. Sterile Water

The following sections apply to tests for *Sterile Water for Injection*, *Sterile Purified Water*, *Sterile Water for Irrigation*, *Sterile Water for Inhalation*, ▲and any other monographs that specify this section. The sterile waters are derived from *Purified Water* or *Water for Injection*, and therefore have been determined to be compliant with the *Bulk Water* (section 1) requirements before being stored and sterilized in the container.▲ (USP 1-May-2021)

Follow the requirements ▲for *Container preparation* (section 1.3) and *Other control solutions* (section 1.8). Prepare the *Standard solution* (section 2.4) and the *System suitability solution* (section 2.3) that correspond to the *Limit response* (section 2.7) for the volume of the container being tested as specified in *Table 1* and as described in steps 2 and 4 in *Procedure* (section 2.9).

Table 1. TOC Limit Based on Container Volume

Nominal Container Volume (mL)	Limit 1 (*L1*) (mg/L of carbon)	Limit 2 (*L2*)[a] (mg/L of carbon)
≤5	32.00	48.00
>5 and ≤100	24.00	36.00
>100	8.00	12.00

[a] *Limit 2* concentrations are utilized to determine the system suitability requirements for the container volume being tested.

2.1 Instrument requirements: The suitability of the instrument must be periodically demonstrated as described below. In addition, it must have a manufacturer's specified limit of detection of 0.10 mg/L (0.10 ppm) or lower of carbon.▲ (USP 1-May-2021)

2.2 Reagent water: Use water with a TOC level of NMT 0.50 mg/L. [NOTE—▲See *General Notices, 8.230.30 Water in a Compendial Procedure*.▲ (USP 1-May-2021) A conductivity requirement may be necessary in order to ensure method reliability.]

2.3 System suitability solution: Dissolve an accurately weighed quantity of USP 1,4-Benzoquinone RS in *Reagent water* (section 2.2) to obtain a solution with a concentration ▲that corresponds to the container volume being tested, as specified in *Table 2*:

Table 2. System Suitability Solution Based on Container Volume

Nominal Container Volume (mL)	1,4-Benzoquinone (▲mg▲ (ERR 1-May-2021)/L)	Equivalent Carbon Concentration (mg/L of carbon)
≤5	72.00	48.00
>5 and ≤100	54.00	36.00
>100	18.00	12.00▲ (USP 1-May-2021)

2.4 Standard solution: Unless otherwise directed in the individual monograph, dissolve an accurately weighed quantity of USP Sucrose RS in the *Reagent water* (section 2.2) to obtain a solution with a concentration ▲that corresponds to the *Standard solution* (section 2.4), measured for the container volume being tested, as specified in *Table 3*:

Table 3. Standard Solution Based on Container Volume

Nominal Container Volume (mL)	Limit 1 (*L1*)		Limit 2 (*L2*)	
	Sucrose Concentration (mg/▲L▲ (ERR 1-May-2021))	Equivalent Carbon Concentration (mg/L of carbon)	Sucrose Concentration (mg/▲L▲ (ERR 1-May-2021))	Equivalent Carbon Concentration (mg/L of carbon)
≤5	76.00	32.00	114.00	48.00
>5 and ≤100	57.00	24.00	85.50	36.00
>100	19.00	8.00	28.50	12.00

2.5 Reagent water control: Use a suitable quantity of *Reagent water* (section 2.2) obtained at the same time as those used in the preparations of the *Standard solution* and the *System suitability solution* (section 2.3).▲ (USP 1-May-2021)

2.6 Water sample: Obtain ▲water samples▲ (USP 1-May-2021) that suitably reflect the quality of ▲the sterile water batch being tested. [NOTE—See *Container preparation* (section 1.3).]▲ (USP 1-May-2021) Before opening ▲the water packages to remove water samples for analysis,▲ (USP 1-May-2021) vigorously agitate the packages to homogenize ▲any TOC residues that may be present in packages. For small packages, several▲ (USP 1-May-2021) packages may be required in order to collect a sufficient water ▲volume▲ (USP 1-May-2021) for analysis. ▲Otherwise test water samples individually.

2.7 Limit response: Measure the TOC of the *Reagent water control* (section 2.5) and record the response (r_W). Also measure the TOC of the *Standard solution* (section 2.4) prepared at concentrations corresponding to the appropriate *Limit 1*, and, if required for step 4 in *Procedure* (section 2.9), *Limit 2* values from *Table 1* for the container volume being tested. The values in this table are the TOC limits based on container volume. Finally, record the instrument response to each of the *Standard solutions* (section 2.4) for *Limit 1* (r_{S1}) and, if required, *Limit 2* (r_{S2}) from *Table 1*.

Calculate the corrected instrument response to the *Standard solutions* prepared at the *Limit 1* (r_{L1}) or *Limit 2* (r_{L2}) concentrations, as appropriate, by subtracting the *Reagent water control* response (r_W) from the *Limit 1 Standard solution* response (r_{S1}) and, if required, the *Limit 2 Standard solution* response (r_{S2}):

$$r_{L1} = r_{S1} - r_W$$

and if required:

$$r_{L2} = r_{S2} - r_W$$

r_{S1} = instrument response to the *Limit 1 Standard solution*
r_{S2} = instrument response to the *Limit 2 Standard solution*
r_W = instrument response to the *Reagent water control*▲ (USP 1-May-2021)

2.8 System suitability: ▲Prepare the *Standard solution* (section 2.4) at the TOC concentrations corresponding to the *Limit 2* in *Table 3* for the container volume being tested. Prepare the *System suitability solution* (section 2.3) according to *Table 2* for the container volume being tested. Measure the TOC of the *Reagent water control* (section 2.5) in the instrument, and record the response (r_W). Measure the TOC of the *Standard solution* (section 2.4), and record the response (r_S). Calculate the corrected *Standard solution* response ($r_S - r_W$), by subtracting the *Reagent water control* response (r_W) from the *Standard solution* response (r_S). Measure the TOC of the *System suitability solution* (section 2.3) in the instrument, and record the response (r_{SS}). Calculate the corrected *System suitability solution* response ($r_{SS} - r_W$) by subtracting the *Reagent water control* response (r_W) from the *System suitability solution* response (r_{SS}) (section 2.3). Calculate the percent response efficiency (r_E):

$$r_E = 100 \times [(r_{SS} - r_W)/(r_S - r_W)]$$

r_{SS} = instrument response to the *System suitability solution*
r_W = instrument response to the *Reagent water control*
r_S = instrument response to the *Standard solution*

The system is suitable if the percent response efficiency is NLT 85% and NMT 115%. The suitability of the instrument must be periodically demonstrated.▲ (USP 1-May-2021)

2.9 Procedure
▲

1. Measure the TOC of the *Water sample* (section 2.6) and record the response (r_U).
2. Compare the r_U to the corrected instrument response (r_{L1}) for *Limit 1* [see *Limit Response* (section 2.7)] for the appropriate nominal container volume.
3. If r_U is NMT r_{L1}, then the *Water sample* (section 2.6) meets the requirements and the test is completed.
4. If r_U is greater than r_{L1}, then compare r_U from step 1 to r_{L2} for the appropriate nominal container volume.
5. If r_U is greater than r_{L2}, then the *Water sample* does not meet the requirements and the test is completed.
6. If r_U is greater than r_{L1} but NMT r_{L2}, then use suitable analytical procedures appropriate for the intended use to identify and quantify each individual organic impurity exceeding a concentration of 0.20 mg/L of carbon.

7. If there are no individual impurities that exceed 0.20 mg/L of carbon, then the *Water sample* (section 2.6) meets requirements and the test is completed.
8. If there are individual impurities that exceed 0.20 mg/L of carbon, then evaluate them for safety at the concentrations found in this testing.
9. If the evaluation of the organic impurities is deemed safe, then the *Water sample* (section 2.6) meets the requirements and the test is completed.
10. If the evaluation of the organic impurities is deemed to impact patient safety, then the *Water sample* (section 2.6) does not meet the requirements and the test is completed.

▲ (USP 1-May-2021)

ADDITIONAL REQUIREMENTS

- **USP REFERENCE STANDARDS** ⟨11⟩

USP 1,4-Benzoquinone RS
USP Sucrose RS