BRIEFING

〈**643**〉 **Total Organic Carbon,** *USP 30* page 257. This chapter has been modified in response to inquiries regarding the following topics: (1) to address the relationship between TOC and microbiological activity, (2) to provide guidance to the analyst on the method, and (3) to provide emphasis on the allowance of on-line measurements.

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Change to read:

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.■2S (*USP31*)

A number of acceptable methods exist for analyzing TOC. This chapter does not ~~limit or prevent alternative~~

■endorse, limit, or prevent any■2S (*USP31*) technologies from being used, but

■this chapter■2S (*USP31*) 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. ~~The *Standard Solution* is a theoretically easy-to-oxidize solution that gives an instrument response at the attribute limit. The analytical technology is qualified by challenging the capability of the instrument using a theoretically difficult-to-oxidize solution in the system suitability portion of the method.~~

~~Analytical technologies utilized to measure TOC share the objective of completely oxidizing the organic molecules in an aliquot of sample water to carbon dioxide (CO_2), measuring the resultant CO_2 levels, and expressing this response as carbon concentration. All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO_2 and bicarbonate, and the CO_2 generated from the oxidation of organic molecules in the sample.~~

~~Two general approaches are used to measure TOC. One approach determines TOC by subtracting the measured inorganic carbon (IC) from the measured total carbon (TC), which is the sum of organic carbon and inorganic carbon:~~

~~TOC = TC − IC.~~

~~The other approach first purges the IC from the sample before any carbon measurement is performed. However, this IC purging step also purges some of the organic molecules, which can be retrapped, oxidized to CO_2, and quantitated as purgeable organic carbon (POC). The remaining organic matter in the sample is also oxidized to CO_2 and quantitated as nonpurgeable organic carbon (NPOC). In this approach, TOC is the sum of POC and NPOC:~~

~~TOC = POC + NPOC.~~

~~In pharmaceutical waters, the amount of POC is negligible and can be discounted. Therefore, for the purpose of this methodology, NPOC is equivalent to TOC.~~

■TOC measurement technologies should discriminate the inorganic carbon, which may be present in the water from sources such as dissolved CO_2 and bicarbonate, from any CO_2 that may be generated during the analysis of the organic components. In addition to other requirements listed below, the *System Suitability* test is the challenge to the TOC technology.■2S (*USP31*)

Change to read:

Apparatus Requirements—This test method is performed either as an on-line test or as an off-line laboratory test using a calibrated instrument.

■On-line TOC measurements for bulk-produced waters such as *Purified Water, Water for Injection,* and *Pure Steam* condensate have the advantage of providing real-time measurements and opportunities for real-time process control and decisions, in addition to recording the TOC quality attribute for release of water to production. Due to the high purity of these waters, off-line measurements of bulk waters have the disadvantage of being impacted adversely by the sampling method, sampling container, and uncontrollable environmental factors such as organic vapors. Because water production could be a batch operation or a continuous operation, the nature of the water production should be considered when determining if off-line or on-line measurement is to be used.■2S (*USP31*)

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.

Change to read:

~~**Glassware Preparation—**~~

■**Container Preparation**—■2S (*USP31*) Organic contamination of ~~glassware~~

■containers■2S (*USP31*) results in higher TOC values. Therefore, use ~~glassware and sample~~

■■2S (*USP31*) 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.

Change to read:

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 ~~about~~

■ ■2S (*USP31*)
1.2 mg of sucrose per L (0.50 mg of carbon per L).

Change to read:

Test Solution—~~[NOTE—Use extreme caution when obtaining samples for TOC analysis. Water samples can be easily contaminated during the process of sampling and transportation to a testing facility.] Collect the *Test Solution* in a tight container with minimal head space, and test in a timely manner to minimize the impact of organic contamination from the closure and container.~~

■FOR OFF-LINE TESTING—Use caution when obtaining samples for TOC analysis. Water samples can be easily contaminated during the process of sampling and transportation to a testing facility. Collect the *Test Solution* in a tight container with minimal head space, and test in a timely manner to minimize the impact of organic contamination from the closure and container.

FOR ON-LINE TESTING—Use caution when connecting the on-line TOC measurement system to the water production system. The piping and measurement system may require substantial time to rinse depending on many factors.■2S (*USP31*)

Change to read:

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.■2S (*USP31*)

Change to read:

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 response efficiency for the *System Suitability Solution* by the formula:

$$100[(r_{ss} - r_w) / (r_S - r_w)]$$

■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.*■2S (*USP31*)
The system is suitable if the response efficiency is not less than 85% and not more than 115% of the theoretical response.

Change to read:

Procedure—Perform the test on the *Test Solution,* and record the response, r_U. The *Test Solution* meets the requirements if r_U is not more than the limit response, $r_S - r_w$. This method also can be performed ~~alternatively~~

■ ■2S (*USP31*)
using on-line

■or off-line ■2S (*USP31*)
instrumentation that ~~has been appropriately calibrated, standardized, and has demonstrated acceptable system suitability. The acceptability of such on-line instrumentation for quality attribute testing is dependent on its location(s) in the water system. These instrument location(s) and responses must reflect the quality of the water used.~~

■meets the *Apparatus Requirements.* For both on-line and off-line measurements, the suitability of instrumentation for quality control testing is also dependent on the sampling location(s) in the water system. The selected sampling location(s) must reflect the quality of the water used.■2S (*USP31*)