# USP <643> Total Organic Carbon changes for sterile packaged water effective May 2021

## background

The United States Pharmacopeia (USP) specifies regulations for pharmaceutical manufacturing and testing to ensure safe and effective drug products. USP <643> Total Organic Carbon (TOC) pertains to requirements for testing pharmaceutical grade water.

TOC is an important quality attribute that contributes to understanding water quality before use in critical applications. TOC is central to process control and patient safety and therefore stringent testing requirements are enforced by regulatory bodies around the world.

Effective May 2021, USP <643> will require that packaged water has container volume-dependent TOC limits and system suitability concentrations. Sievers* M9 TOC Analyzers and SUEZ standards comply with these revisions. Whether using the Sievers M9, or another instrument, now is the time to scrutinize technology and processes used to test TOC.

This application note and the USP changes discussed below are limited in scope to packaged water. Bulk waters (i.e., purified water or water for injection made via a site water system) are not affected by the USP <643> changes and will continue to use the standard 500 ppb system suitability sets and limits.

## changes to acceptance criteria & system suitability

Previously, sterile water had a standardized limit and system suitability concentration of 8 ppm. This concentration was applied to all packaged water regardless of container size.

USP <643> Total Organic Carbon will be revised for sterile water in containers. It is important to note that these methodology changes will only affect analysis of sterile, packaged water and not bulk water. Acceptance criteria and system suitability for sterile packaged water will change to be dependent on container volume.

As container size decreases, there is more packaging surface area relative to water which can lead to increased leaching from container to water and more TOC. The USP has taken this into consideration and allowed for higher limits on containers with increased risk of leaching. Nominal container volumes and corresponding limits are shown in **Table 1**.

**Table 1. Standard Solution Concentrations for Limit 1 and Limit 2**

| | Standard Solution - Limit 1 | Standard Solution - Limit 2 | System Suitability Solution |
|---|---|---|---|
| **Nominal Container Volume (mL)** | **Concentration of Carbon from Sucrose (mg/L C, or ppm C)** | **Concentration of Carbon from Sucrose (mg/L C, or ppm C)** | **Concentration of Carbon from 1,4-Benzoquinone (mg/L C, or ppm C)** |
| **≤5** | 32.00 | 48.00 | 48.00 |
| **>5 and ≤100** | 24.00 | 36.00 | 36.00 |
| **>100** | 8.00 | 12.00 | 12.00 |

The limit of TOC is changing from a defined value of 8.0 mg/L C (8 ppm) to a variable limit determined by container volume. USP <643> requirements for sterile water will still require the instrument to have a specified range from 0.10 mg/L up to the highest range for TOC limit for container size. While concentrations for packaged water system suitability have changed, determining system suitability pass/fail maintains the same calculations.

The procedure section of USP <643> outlines testing of samples. This testing procedure has changed from a pass/fail limit test to a staged testing procedure, as outlined below. Note that system suitability at Limit 2 will need to be performed on some frequency prior to testing samples.

When testing water samples against limits for the defined container size:

- If sample is less than Limit 1 (see **Table 1**), then sample passes and test is complete.
- If sample is greater than Limit 1 and less than Limit 2 (see **Table 1**), then proceed to <643> step 2.9(6.) to identify and quantify organic impurities exceeding 0.20 mg/L of Carbon.
- If sample is greater than Limit 2 (see **Table 1**), then sample fails and test is complete.

## SUEZ is here to help

The Sievers M9 TOC Analyzer along with new system suitability sets will provide full compliance to these changes. SUEZ will provide standard concentrations and procedures to align with required concentrations defined in USP <643> as shown in **Table 2**.

**Sterile water suitability sets will include:**

- Reagent Water
- Standard Solution, Limit 1
- Standard Solution, Limit 2
- System Suitability Solution

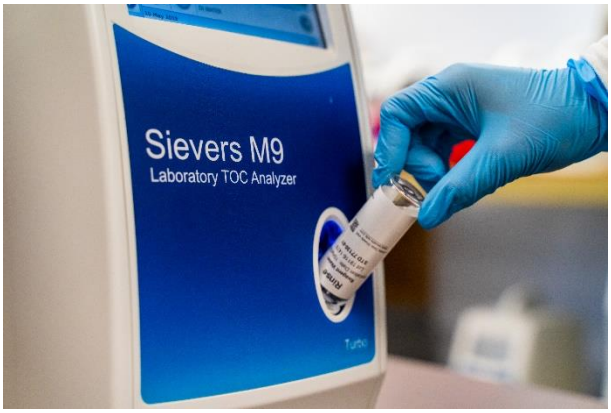


**Table 2. SUEZ system suitability part numbers**

| Nominal Container Volume (mL) | Part Number |
|---|---|
| **≤5** | STD 77007-01 |
| **>5 and ≤100** | STD 77006-01 |
| **>100** | STD 77005-01 |

The concentrations included in each set will be based on the nominal container volume. The standards included in these sets will be used to determine Limit 1, Limit 2, and response efficiency. Limit 1 and 2 are determined by subtracting the response of the reagent water from the response of the standard solutions. Response efficiency will be calculated as in the past, using the Limit 2 standard solution.

When using the Sievers M9 TOC Analyzer for pharmaceutical grade water testing, system protocols are used to automate system suitability for 500 ppb and 8 ppm requirements. The M9 is still capable of executing the new system suitability sets; however, the current version of software does not have a system protocol available for automating analysis and calculating pass/fail criteria. Until a future software version can be implemented to accommodate system protocols for new system suit requirements, manual protocols should be built as outlined below in **Table 3** using recommended reagent flow rates noted in **Table 4**.

**Table 3. Example protocol configuration for container volumes of >100mL**

| Step # | Rack | Position | Sample Name | Lot # | Type | Reps | Rejects | Acid Rate | Oxid Rate | Flush Time | Turbo | ICR | TOC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | R1 | 1 | Rw, >100mL container | | Sample | 5 | 2 | 1.0 µL/min | 2.5 µL/min | 240 sec | Off | Off | On |
| 2 | R1 | 2 | Std Limit 1, >100mL | | Sample | 4 | 1 | 1.0 µL/min | 2.5 µL/min | 240 sec | Off | Off | On |
| 3 | R1 | 3 | Std Limit 2, >100mL | | Sample | 4 | 1 | 1.0 µL/min | 2.5 µL/min | 240 sec | Off | Off | On |
| 4 | R1 | 4 | System suit, >100mL | | Sample | 4 | 1 | 1.0 µL/min | 2.5 µL/min | 240 sec | Off | Off | On |

**Table 4. Recommended acid and oxidizer flow rates**

| Nominal Container Volume (mL) | Oxidizer Flow Rate | Acid Flow Rate |
|---|---|---|
| **≤5** | 9 µL/min | 1.0 µl/min |
| **>5 and ≤100** | 5 µl/min | 1.0 µl/min |
| **>100** | 2.5 µl/min | 1.0 µl/min |

Pass/fail criteria maintains the same calculation as the previous USP <643> version. With software versions 1.09 and earlier, calculations will not be automated by DataPro2. System suitability pass/fail should be determined manually using the definitions and calculations below.

$r_{SS}$ = Instrument response to the System Suitability Solution (1,4-Benzoquinone)

$r_W$ = Instrument response to the Reagent Water Control

$r_S$ = Instrument response to the Standard Solution, Limit 2 (Sucrose)

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

**To pass suitability, response efficiency ($r_e$) must be no less than 85% and no more than 115%.**

## summary

Testing quality of pharmaceutical grade water is not only important for quality and safety, but it is strictly enforced by regulatory bodies around the world such as USP.

In the case of TOC testing, USP <643> prescribes instrumentation, testing, and acceptance limit criteria that must be adhered to for compliant TOC analysis. USP requirements are living documents and can be revised to better fit industry needs or improve safety of products.

USP <643> revisions for sterile packaged water will require system suitability and acceptance criteria to be contingent on container volumes. These changes are specific to packaged water which breaks volumes into three brackets as noted in **Table 1**.

The Sievers M9 can fully support these changes with analytical range, accuracy, precision, and data integrity. Additionally, as shown in **Table 2**, SUEZ has produced new system suitability standard sets to aid customers in achieving total compliance to these changes which will be effective May 2021. With these changes, it is important to examine technology and procedures to make sure TOC testing is up to regulatory expectations. In addition to instrumentation, standards, and consumables, SUEZ's team of experts is ready to address questions and concerns!





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