USP <643> Total Organic Carbon: Update for Sterile Water Procedure (Effective May 1, 2021)

Steve Proffitt, Applications Chemist; Teledyne Tekmar

Objective

To explain the May 21, 2021 changes to United States Pharmacopeia (USP) Method <643> affecting the sterile water procedure, and demonstrate that the Teledyne Tekmar Fusion UV/Persulfate TOC analyzer can comply with these updates.

Background

USP <643> provides guidelines and requirements for TOC analysis of bulk water and packaged sterile water. This method includes a System Suitability Test that compares the recovery of a Standard Solution (r_s) of sucrose (a relatively easy compound to oxidize) to a System Suitability Solution (r_{ss}) of 1,4-benzoquinone (a difficult to oxidize compound). The response of Reagent Water (r_w) is subtracted from the response of each solution, to yield corrected responses. The corrected responses are then compared and must be within 15% of each other to verify the system will sufficiently oxidize organic carbon within different compounds. The Response Efficiency must be between 85% and 115% for the results of the Bulk and Sterile Standards to meet USP <643> requirements using the equation in Figure 1.

Figure 1 Equation from USP <643> to Calculate % Response Efficiency.

% Response Efficiency = $100(r_{SS} - r_W)/(r_S - r_W)$
Where: • 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 (Sucrose)

In 2007 Teledyne Tekmar published the application note, "Simplifying the Process: Automated USP 643 / EP 2.2.44 Purified Water and Water for Injection Testing Using a Next Generation TOC Analyzer" to demonstrate the Fusion's ability to easily pass USP Method <643> requirements with 0.500 mg/L carbon standards. In 2017 we published USP Bulk & Sterile Water Using the Teledyne Tekmar Fusion UV/Persulfate TOC Analyzer in response to updates to USP Method <643>, including the Sterile Water concentration requirement of 8.000 ppmC.

May 1, 2021 Update to USP <643>

Prior to the May 01, 2021 update, packaged sterile water had a standardized limit and system suitability concentration of 8.000 ppmC. This concentration was applied to all sterile water regardless of container size. With the May 01, 2021 update, acceptance criteria for system suitability for all packaged sterile water has changed to be dependent on container size.

Note: This update does not affect the methodology and acceptance criteria for bulk water. The standard solution and system suitability solution used for bulk water remains at a concentration of 0.500 mg/L carbon.

Container size can directly influence the level of TOC that may leach from the container into the water. A small container will have a higher surface area to water ratio, consequently increasing the possibility of higher TOC levels from container leaching. Table I shows changes the USP has implemented due to higher leaching probability in relation to container size.

Sales/Support: 800-874-2004 • **Main**: 513-229-7000
4736 Socialville Foster Rd., Mason, OH 45040
www.teledynetekmar.com

Table I TOC Limit Based on Container Volume		
Nominal Container Volume (mL)	**Limit 1 (mg/L of Carbon)**	**Limit 2 (mg/L of Carbon)**
≤5	32.00	48.00
>5 and ≤100	24.00	36.00
>100	8.00	12.00
Note: Limit 2 concentrations are used to determine the system suitability requirements for the container volume being tested.		

Table II shows the instrumentation requirements for bulk water and sterile water along with the published limit of detection (LOD) capability of the Fusion UV/Persulfate TOC Analyzer.

Table II Instrument LOD Requirements and Fusion LOD Capability		
Bulk Water Requirement	**Sterile Water Requirement**	**Fusion LOD Capability**
≤0.05 mg/L	≤0.10 mg/L	0.0002 mg/L

Table III shows the requirements for reagent water used for the procedures for bulk water and sterile water. Also listed is the practical quantification limit (PQL) of the Fusion UV/Persulfate TOC Analyzer.

Table III Reagent Water Requirements and Fusion PQL Capability		
Bulk Water Requirement	**Sterile Water Requirement**	**Fusion PQL Capability**
≤0.10 mg/L	≤0.50 mg/L	0.002 mg/L

Instrument Methods

To demonstrate the Fusion's ability to achieve the requirement for reagent water, the Fusion TekLink software's default "TOC Pharmaceutical Water" method is required. This method uses a 9.0 mL sample volume per replicate which allows the Fusion to measure accurately at ppb levels.

Note: The Fusion's default "TOC Pharmaceutical Water" method is also used for meeting the USP <643> bulk water system suitability requirements.

However, to analyze the "Limit 2" concentrations necessary to meet the method's updated sterile water procedure for system suitability, a calibration with an upper limit of 50.0 mg/L is required. To achieve this upper limit, a dilution method must be created.

To create the required dilution method, the Fusion's default "TOC Drinking Water" method was modified by simply changing the "Dilution" parameter to 1:5. This enables the Fusion to have an optimal upper calibration limit of 50.0 mg/L. The 1:5 dilution method parameters are shown in Figure 2.

Sales/Support: 800-874-2004 • **Main**: 513-229-7000
4736 Socialville Foster Rd., Mason, OH 45040
www.teledynetekmar.com

Figure 2 1:5 Dilution Method.

Name: PQ Method 2 (TOC)

Version: v1 Operator: SP (Appslab)
Ver Creation: 2022/03/02 14:06
Comment:

Parameter	Value
SampleVolume	6.0 mL
Dilution	1:5
AcidVolume	1.0 ml
ReagentVolume	1.0 ml
UVReactorPrerinse	On
UVReactorPrerinseVolume	5.0
NumberOfUVReactorPrerinses	1
ICSpargeTime	1.00 mins
DetectorSweepFlow	500 ml/min
PreSpargeTime	0.20 mins
SystemFlow	200 ml/min

1:5 Dilution Method Calibration Results

The results from the calibration established a coefficient of correlation (r^2) of 0.99995. While a coefficient of correlation limit is not required by USP <643>, it is important to have an r^2 value of >0.995 to attain accurate System Suitability results.

Figure 3 1:5 Dilution Method Calibration Results.

Name: PQ Method 2 (TOC)

Version: v2
Ver Creation: 2022/03/02 16:37
Comment:
Operator: SP (Appslab)
Basic Analysis Type TOC

Calibration curve formula: TOC: y = 8.826x + 11.878
r^2 value: TOC: r^2 = 0.99995

Basic Analysis Type: TOC

Sample ID	Y Raw Value	X Expected	Message	End Time
5.000 ppm	55.9813	5.0000		2022/03/02 15:14
10.000 ppm	99.1020	10.0000		2022/03/02 15:36
25.000 ppm	234.2263	25.0000		2022/03/02 15:59
50.000 ppm	452.5277	50.0000		2022/03/02 16:21

Reagent Water Results

Reagent water was analyzed using a calibration created using the Fusion's default "TOC Pharmaceutical Water" method. The r^2 value for this calibration was 0.99997. The analysis result for reagent water was 0.0634 mg/L C. To pass the USP <643> requirement, the reagent water must be less than 0.500 mg/L C.

Sterile Water System Suitability Results

Sterile water concentrations required are represented by 12.0, 36.0 and 48.0 mg/L carbon for both sucrose and 1,4-benzoquinone standards. Standards were prepared according to USP <643> guidelines. For each concentration, the sucrose and 1,4-benzoquinone must have a response efficiency within 85-115% of each other using the equation shown in Figure 1. The accurate response efficiencies shown in Table IV confirm how effectively the Fusion analyzes both easy and difficult to oxidize compounds at concentrations ranging up to 48.0 mg/L as required by the revised USP <643>.

Sales/Support: 800-874-2004 • **Main**: 513-229-7000
4736 Socialville Foster Rd., Mason, OH 45040
www.teledynetekmar.com

Table IV Sterile Water System Suitability Test Results			
r_W = Instrument Response to the Reagent Water Control (mg/L C) = 0.0634			
r_S = Instrument Response to the Standard Solution (Sucrose)			
Concentration (mg/L C)	12.00	36.00	48.00
Analysis Result (mg/L C)	12.04	36.97	48.17
r_{SS} = Instrument Response to the System Suitability Solution (1, 4 Benzoquinone)			
Concentration (mg/L C)	12.00	36.00	48.00
Analysis Result (mg/L C)	11.75	35.96	46.49
Response Efficiency	**97.58**	**97.27**	**96.51**

Conclusion

The Teledyne Tekmar Fusion UV/Persulfate TOC Analyzer successfully analyzed the revised USP <643> sterile water system suitability standard concentrations and was well within the requirement of 85% - 115%.

References

1. United States Pharmacopeia <643> Total Organic Carbon [Revised: 01-May-2021].

Contact Us!

See how the Teledyne Tekmar Fusion UV/Persulfate Analyzer can help you comply with pharmaceutical and/or environmental standards. Contact a sales representative at 1.800.874.2004 or visit http://www.teledynetekmar.com/contact/sales-contacts. See genuine customer reviews of the Fusion at http://www.selectscience.net.

Sales/Support: 800-874-2004 • **Main**: 513-229-7000
4736 Socialville Foster Rd., Mason, OH 45040
www.teledynetekmar.com