TELEDYNE TEKMAR
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Pharmaceuticals

Applications for TOC Analysis

Today's pharmaceutical laboratories are tasked with providing a wide array of analytical analyses for every stage of the production process, from ensuring the cleanliness of the process equipment and the raw ingredients to quality control of the finished products. Many of these test and regulations are published in pharmacopeias.

Total Organic Carbon (TOC) analyzers play a significant role in the pharmaceutical testing laboratories and manufacturing facilities as described in the pharmacopeias. Water is a major excipient and solvent used in pharmaceutical manufacturing and cleaning processes. TOC analyzers are used to measure the amount of organic carbon that is present in water used within the pharmaceutical process.

THE PHARMACEUTICAL INDUSTRY'S NEED FOR TOTAL ORGANIC CARBON ANALYSIS

Bulk water, sterile water, purified water and water for intravenous injection are vital for drug preparation. The water for these applications must have carbon values in the ppb or even single digit ppb range. Producing and ensuring the cleanliness of this water entails extremely strict quality control and precise analytical equipment.

The United States Pharmacopeia (USP), European Pharmacopeia (EP) and Japanese Pharmacopeia (JP) have promoted TOC analysis as the procedure to verify purified water, water for intravenous injection and other water sources used in the pharmaceutical process. These tests are used to ensure the water meets lofty standards outlined in these monographs.

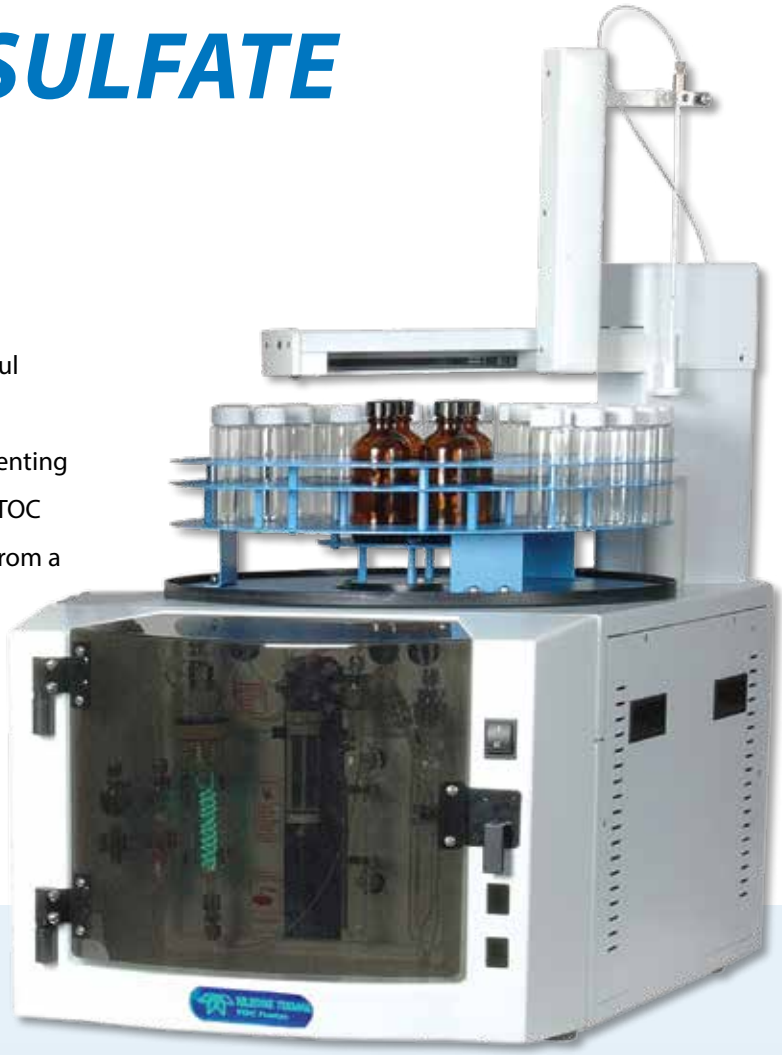
METHODS

- USP <643> - Method for Measuring TOC in Water Used for Pharmaceutical Applications
- EP 2.2.44 - Total Organic Carbon in Water for Pharmaceutical Use
- JP 2.59 Test for Total Organic Carbon

Before starting TOC analysis, a system suitability test must be run.

Methods	System Suitability
USP <643> - Method for Measuring TOC in Water Used for Pharmaceutical Applications	Test that compares the recovery of a Standard Solution (rs) of 0.500 ppmC sucrose (a relatively easy compound to oxidize) to a System Suitability Solution (rss) of 0.500 ppmC 1,4-benzoquinone (a difficult to oxidize compound). The response of Reagent Water (rw) must be less than 100 ppbC and is subtracted from each of these solutions' responses to yield a corrected response. The corrected responses are then compared and must be within 15% of each other to confirm the system will thoroughly oxidize organic carbon compounds with differing affinities for oxidation. The Response Efficiency must meet the 85% - 115% requirement Formula Used to Calculate the Response Efficiency. **% Response Efficiency = 100[(rss-rw)/(rs-rw)]**
EP 2.2.44 - Total Organic Carbon in Water for Pharmaceutical Use	
JP 2.59 Test for Total Organic Carbon	JP requires that a TOC Analyzer be validated to recover ≥ 450ppb Carbon from 500ppb Dodecylbenzenesulfonic acid standard.

FUSION UV/PERSULFATE ANALYZER



The Fusion Total Organic Carbon (TOC) Analyzer utilizes powerful Ultra Violet (UV) Persulfate oxidation allowing superior carbon liberation from even the most challenging matrices. By implementing the Static Pressure Concentration (SPC) technology, the Fusion TOC Analyzer is able to achieve unprecedented low-end sensitivity from a Non-Dispersive Infrared (NDIR) detector.

The Fusion TOC Analyzer is designed to offer productivity for a wide variety of applications.

ADVANTAGES OF THE FUSION

- Auto-calibration for unattended calibration monitoring
- Intellidilution for automatically diluting a sample back into calibration range
- Tools for 21 CFR Part 11 Compliance
- Turn-key method development
- Exportable reports in user-definable formats including metadata
- User friendly software
- Pre-programmed method features for pharmaceutical applications
- Self-diagnostic capabilities including leak check
- Mass flow controller for reduced gas consumption and enhanced flow control

UNPARALLELED RESULTS

The Fusion is designed to determine the carbon content in water and other solutions. Using safe and proven UV persulfate oxidation of carbonaceous material to carbon dioxide (CO_2) followed by NDIR detection of the CO_2 product, the Fusion is sensitive from 0.2ppbC - 4,000ppmC. Varieties of carbon measurements can be independently determined by selecting a pre-defined instrument method, such as:

- Total Carbon (TC)
- Inorganic Carbon (IC)
- Total Organic Carbon (TOC = TC-IC)
- Non-Purgeable Organic Carbon (NPOC or TOC by sparging)

To determine TOC by the NPOC method, the Fusion uses a syringe driver and 7-port valve to accurately transfer samples and reagents to the reactor. It then uses carrier gas to transfer the reaction product (CO_2) from the sample either to vent or to the NDIR detector in the following sequence:

1. Removal and venting of IC and POC by acidification and sparging in the IC sparger.
2. Following IC removal, an aliquot of the sparged sample is transferred to the UV reactor and persulfate reagent is added to oxidize the organic carbon, based on the following chemical reactions:
   a. Free radical oxidants formed
   b. Excitation of organics
   c. Oxidation of organics

The oxidation products in Step 2 are swept into the CO_2 selective NDIR detector.

The exit valve from the NDIR is closed to allow the detector to become pressurized. Once the gases in the detector have reached equilibrium, the concentration of the CO_2 is analyzed. The pressurization of the sample gas stream in the NDIR is called Static Pressure Concentration (SPC). It allows for increased sensitivity and precision. SPC measures all of the oxidation products in the sample in one reading, compared to flow-through technology. The output signal is proportional to the concentration of CO_2 in the carrier gas, from the oxidation of the sample.

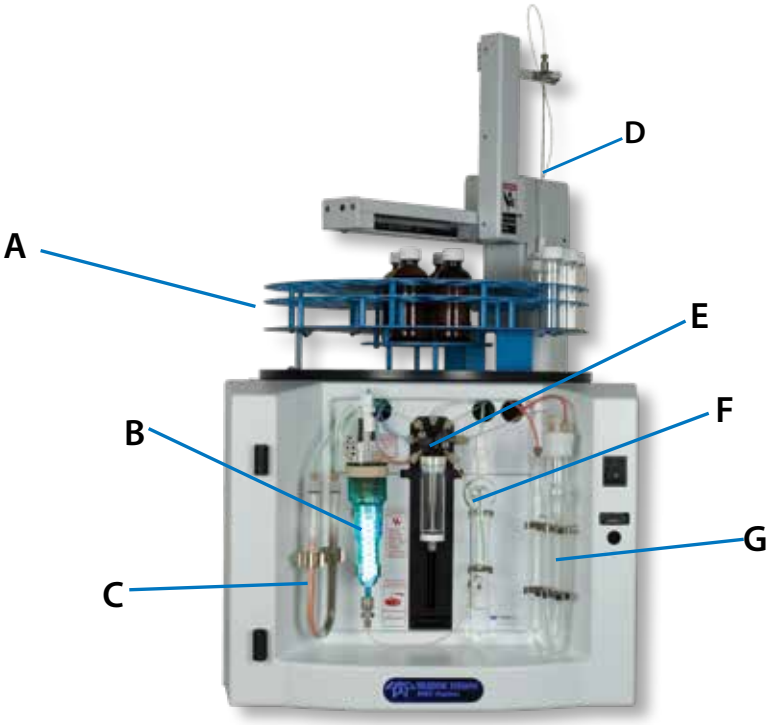
The PC workstation uses the TOC TekLink™ software to control the above sequence of operations, process the detector signal, and report the final concentration of the sample based on linearized, multi-point calibration data.

PHARMACEUTICAL METHODS

- USP <643>
- EP 2.2314
- JP 2.59
- Cleaning Validation
- Water for Injection

FEATURES AND BENEFITS

Permeation Dryer



Note: *Fusion shown with front door removed.*

A. Autosampler - The Fusion has a standard 40mL vial, 75-position integrated autosampler with arobotic arm and carousel for position selection.

B. UV Oxidation Reactor – The UV reactor is composed of a glass vessel and a UV light source. The Fusion introduces the sample and persulfate reagent into the UV reactor. The persulfate reagent, combined with UV light, oxidizes carbon in the sample. Tekmar's improved UV reactor increases sample conservation and improves radiation interaction with water samples and oxidant.

C. Halogen Scrubber - The detector, which measures CO_2, can be affected by halogens. To prevent analytical errors, the halogen scrubber removes chlorine and other halogens from the CO_2 before it enters the detector.

D. Septum Piercing Needle – The needle allows for the use of vial caps with a septa thus eliminating sample exposure time to the atmosphere.

E. Syringe and Valve - The syringe driver is a precision measuring instrument that draws in and dispenses fluid. The syringe driver has a volume delivery range of 125µL to 25mL and sample delivery between 2mL and 10mL depending on the applied method.

F. Moisture Control System (MCS) - The MCS consists of a mist trap and permeation dryer, both of which are designed to remove moisture from the sample. After oxidation of the sample, carrier gas sweeps CO_2 and water vapor out of the UV reaction chamber. Next, the CO_2 travels through the mist trap, where most of the moisture is collected and removed. The gases then travel to the permeation dryer, which removes the rest of the moisture from the sample gas.

G. IC Sparger - The IC Sparger is a glass fritted vessel that holds the sample while purging the Inorganic Carbon (IC) out of the sample and preparing it for analysis. After the addition of acid, purge gas flows through the sparger, removing the IC from the sample. The Fusion can report IC for both IC only and TC-IC modes, or vent it into the atmosphere while in the TOC mode.

ADDITIONAL FEATURES

Mass Flow Controller (MFC) - The MFC regulates either flow or pressure depending on the mode of operation. It allows for higher flows for clean up between samples and allows the user to optimize the sparge flow for each sample. Because of the MFC, the instrument automatically validates the system integrity by recording the pressure each time a sample is run. The MFC also performs pneumatic integrity tests on valves to make sure they are leak tight.

Intellidilution – This intelligent feature detects when a sample is out of range and will dilute it back to within the calibration range. Intellidilution also has the ability to meet individual analytical needs due to pre-set ranges (non-dilution methods only).

Autocalibration – Using a single stock solution, the system will automatically dilute final volumes based on the users linearizing concentration requirements, thus eliminating the need for multiple manual preparations of the calibration standard concentration levels. This feature eliminates the likelihood of human error and minimizes labor time.

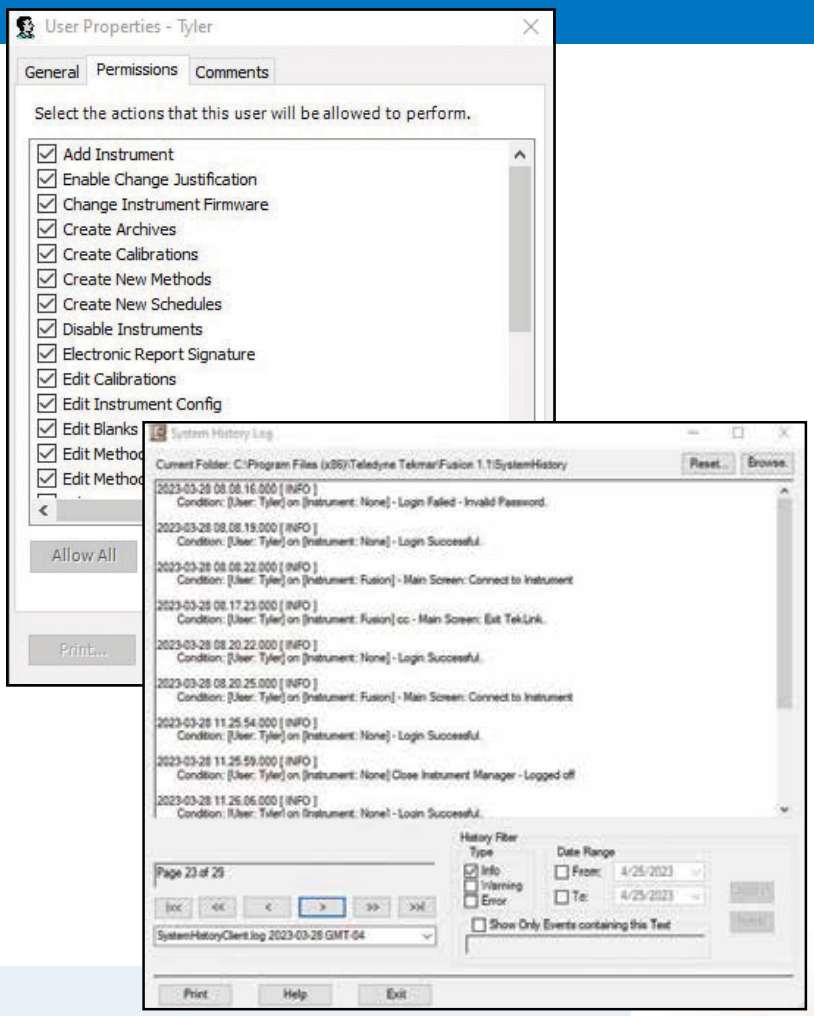
Static Pressure Concentration (SPC) - After the sample oxidizes, it is swept into the detector and pressurized with carrier gas ensuring the entire sample is present. The Non-Dispersive Infrared (NDIR) detector then measures the concentration of carbon dioxide. As a whole, this technology enables the Fusion to reach new levels of detection required by todays demanding analytical requirements.

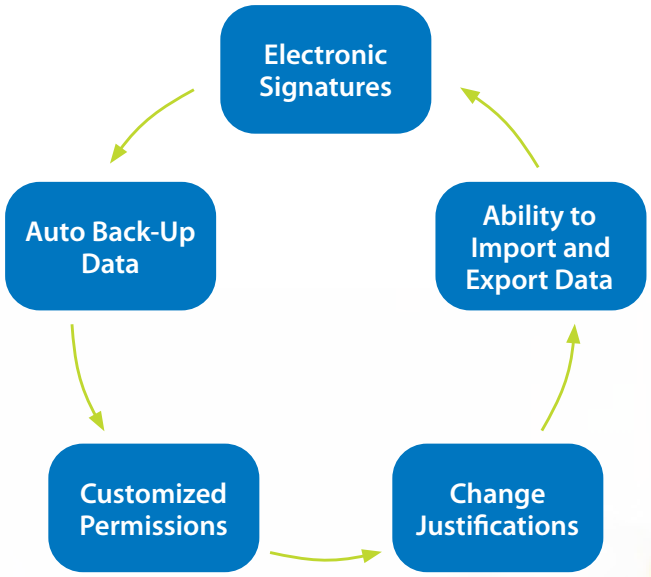
21 CFR 11

OVERVIEW OF FUSION TOC TEKLINK TOOLS FOR 21 CFR 11 COMPLIANCE

Fusion TOC TekLink software provides tools to aid in 21 CFR 11 compliance. This means that:

- User accounts and access privileges are secure.
- Methods, calibrations and schedules are all versioned, user-tracked and archived.
- Report data is secure, versioned, archived and retrieved with audit capability.
- Report data can have electronic signatures attached.
- System history and error logs can be viewed and printed.





NOTE...

The Fusion TOC TekLink software can be used as a tool for 21 CFR 11 compliance, but it should be noted that maintaining the instrument by performing preventative maintenance and replacement of consumables, according to the Fusion user manual, is also a necessary component of complying with 21 CFR 11. Compiance is gained through your auditing authority.

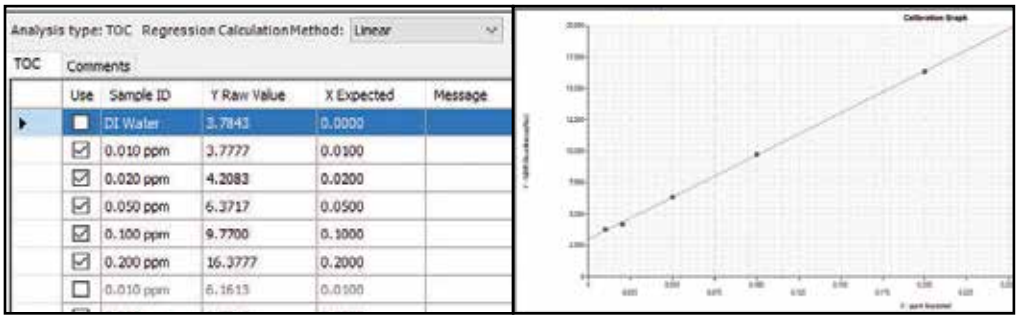
DATA

UNITED STATES PHARMACOPOEIA/EUROPEAN PHARMACOPOEIA

The USP <643> and EP 2.2.44 monographs provide guidelines and requirements for TOC analysis of water for injection and purified water and bulk/sterile water.

A five-point calibration was performed using the Fusion's auto-calibration feature. A 200µg/L standard made from potassium hydrogen phthalate was used to build a calibration range of 10 - 200µg/L. Calibration results are shown below.

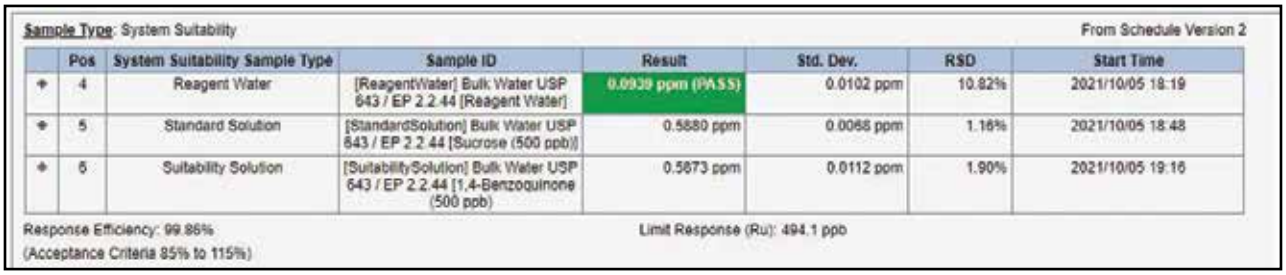
	Pos	BAT	Concentration (ppm)	STD Conc	Dil	Sample ID	Result (Abs)	Std. Dev. (Abs)	RSD
◆	A	TOC	0.0100	0.2 ppmC	1:20	[TOC] TOC Low Level [0.010 ppm]	3.7777	0.1355	3.59%
◆	A	TOC	0.0200	0.2 ppmC	1:10	[TOC] TOC Low Level [0.020 ppm]	4.2083	0.0623	1.48%
◆	A	TOC	0.0500	0.2 ppmC	1:4	[TOC] TOC Low Level [0.050 ppm]	6.3717	0.0379	0.59%
◆	A	TOC	0.1000	0.2 ppmC	1:2	[TOC] TOC Low Level [0.100 ppm]	9.7700	0.0940	0.96%
◆	A	TOC	0.2000	0.2 ppmC	1:1	[TOC] TOC Low Level [0.200 ppm]	16.3777	0.1411	0.86%



Sample ID	Min / Max (% dev)	Result	Std. Dev.	RSD
[TOC] TOC Low Level [0.050 ppm]	0.0425 / 0.0575 (85% / 115%)	0.0468 ppm (PASS)	0.0026 ppm	5.56%
[TOC] TOC Low Level [0.050 ppm]	0.0425 / 0.0575 (85% / 115%)	0.0477 ppm (PASS)	0.0014 ppm	2.90%
[TOC] TOC Low Level [0.050 ppm]	0.0425 / 0.0575 (85% / 115%)	0.0462 ppm (PASS)	0.0012 ppm	2.51%
[TOC] TOC Low Level [0.100 ppm]	0.0850 / 0.1150 (85% / 115%)	0.1011 ppm (PASS)	0.0016 ppm	1.54%
[TOC] TOC Low Level [0.100 ppm]	0.0850 / 0.1150 (85% / 115%)	0.1002 ppm (PASS)	0.0005 ppm	0.48%
[TOC] TOC Low Level [0.100 ppm]	0.0850 / 0.1150 (85% / 115%)	0.0986 ppm (PASS)	0.0021 ppm	2.11%

SYSTEM SUITABILITY RESULTS

0.500ppmC Sucrose and 1,4-benzoquinone system suitability standards were prepared according to EP 2.2.44 guidelines. To pass USP <643> and EP 2.2.44, the reagent water must be less than 0.100ppmC and the sucrose and 1,4-benzoquinone standards must have a response efficiency within 85 - 115%. The response efficiency confirms how closely a difficult to oxidize compound and easy to oxidize compound respond in the system. The Fusion TOC TekLink software calculates response efficiency and identifies passing and failing standards to remove the possibility of human error and expedite workflow.


Sample Type: System Suitability — From Schedule Version 2

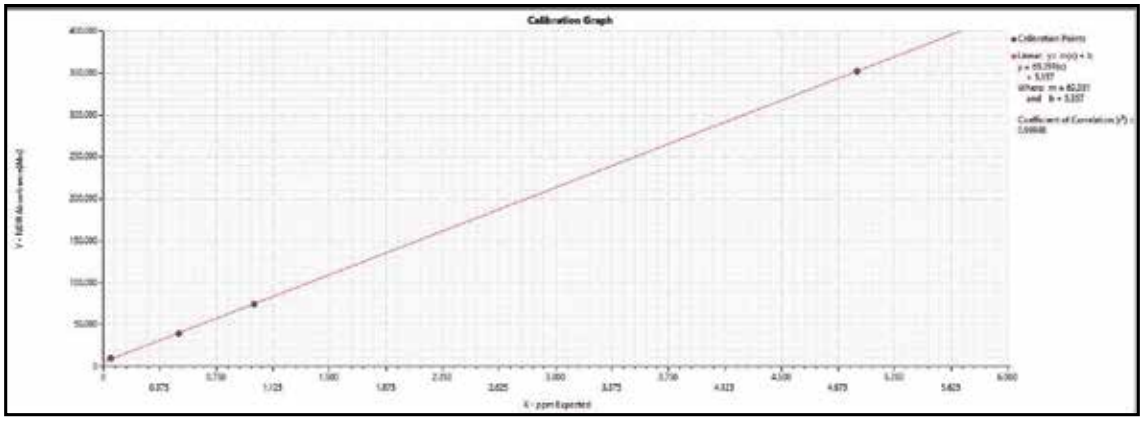
	Pos	System Suitability Sample Type	Sample ID	Result	Std. Dev.	RSD	Start Time
◆	4	Reagent Water	[ReagentWater] Bulk Water USP 643 / EP 2.2.44 [Reagent Water]	0.0939 ppm (PASS)	0.0102 ppm	10.82%	2021/10/05 18:19
◆	5	Standard Solution	[StandardSolution] Bulk Water USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	0.5880 ppm	0.0068 ppm	1.16%	2021/10/05 18:48
◆	6	Suitability Solution	[SuitabilitySolution] Bulk Water USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)	0.5873 ppm	0.0112 ppm	1.90%	2021/10/05 19:16

Response Efficiency: 99.86% (Acceptance Criteria 85% to 115%)
Limit Response (Ru): 494.1 ppb

TOC TekLink Report Showing System Suitability Results and Automated Software Calculations

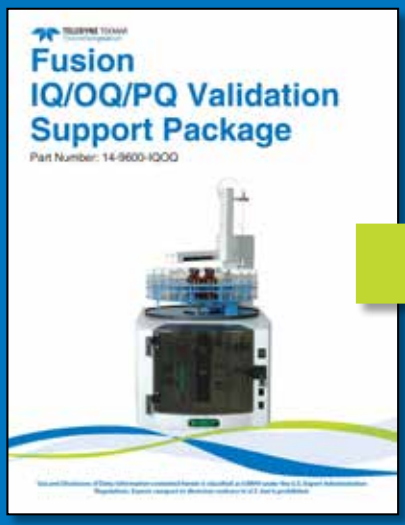
JAPANESE PHARMACOPEIA

JP have promoted TOC analysis as the procedure to verify purified water and water for intravenous injection are free of TOCs and therefore can be used for pharmaceutical purposes. A TOC system is considered suitable, under the JP, if it can recover 90 percent of a 0.5mgC/L sodium dodecylbenzenesulfonate standard.



Sample Name	Concentration (mgC/L)	Std. Dev. (mgC/L)	%RSD
dodecylbenzenesulfonic acid with a carbon concentration of 0.500mg/L	0.503mg/L	0.009	1.85
dodecylbenzenesulfonic acid with a carbon concentration of 0.500mg/L	0.504mg/L	0.012	2.50

FUSION INSTALLATION QUALIFICATION (IQ), OPERATIONAL QUALIFICATION (OQ) AND PERFORMANCE QUALIFICATION (PQ) VALIDATION SUPPORT



- Calibration Check
- Reagent Blank Check
- Specifity Challenge (USP <643>)
- Cross Contamination Challenge
- Intellidilution Check
- User Manager Validation
- Archive Validation

To support 21 CFR 11 compliance, Teledyne Tekmar offers a Fusion UV/Persulfate TOC analyzer IQ/OQ/PQ Validation Support Package (p/n 14-9600-IQOQPQ) performed by a factory certified service engineer.

SPECIFICATIONS

Chemistry:	Photochemical Oxidation via UV-Persulfate[1]
Detector:	Nondispersive Infrared (NDIR) with Static Pressure Concentration (SPC)
Analytical Modes:	TOC (NPOC), TC- IC, TC, IC
Analytical:	Limit of Detection: 0.2ppb Maximum Measurable Concentration: 4,000ppm (sample volume and dilution dependent) Carryover: = 1.0% Cross Contamination Precision*: = 1.0% RSD,+/-2 ppb or +/- 0.02 µgC, typical of a mid-range standard (Whichever is greater over seven replicates). * Analytical performance affected by laboratory water, reagent and gas purity, as well as sample container cleanliness, sample matrix, gas regulator cleanliness and precision, and operator skill.
Complete Process and Analysis Time:	4-8 minutes typical for TOC analysis; Typically 12-22 minutes for Triplicate TOC Analysis
Controller:	Refer to the Supplied Computer Specifications Guide, which can be found on the product page of our website.
21 CFR Part 11 Software Control:	TOC Teklink™ Software is a 21 CFR Part 11 tool for your laboratory compliance
Data Handling:	• Pre-defined Industry Standard Methods and Customized User Defined Methods • Priority samples via schedule interrupt • Real-time and Historical graphical display of NDIR detector data • Reports exportable XML, CSV and HTML format • Recalculation of data, outlier deletions, and precision performance criteria controls • Ability to view historical results from multiple schedules on one graphical display
Calibration:	• Auto-Calibration from Single Stock Standards or User Calibration Standards • Multi-point (Linear or Quadratic) and auto-blanking • Ability to use one calibration curve and blank for entire instruments' analytical range • Auto-Check Standards from Single Stock Standards or User Calibration Standards - Pass / Fail Criteria - Decision Control upon Failure (Halt, Re-Calibrate, or Continue)
Other Features:	• Auto-System Suitability with Performance Measurements • Auto-dilution of samples/standards • Validation Support Package Available • Pre-programmed point and click method setup • Programmable flow rate and pressure control and monitoring • Auto-Leak Check • Automatic shutdown/standby • Self-cleaning sample handling process that cleans reactor chambers on every repetition • Intellidilution
Official Methods:	EPA 415.1- 415.3, 9060A, Standard Method 5310C, ASTM D4779 and D4839, and prENV 13370, Cleaning Validation / USP TOC Method <643> / EP 2.2.44 / JP
Dimensions:	18 inches (45.7 cm) W x 24.5 inches (62.2 cm) D x 32 inches (81.3 cm) H
Carrier Gas Supply:	99.99% pure nitrogen cylinder or 99.9% pure nitrogen generator
Inlet Carrier Gas Pressure:	65 to 100 psi

[1]UV Lamp contains Mercury, Do Not Put In Trash. Recycle or Dispose as Hazardous Waste.

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