

GE  
Water & Process Technologies  
Analytical Instruments

# Sievers\* 500 RL On-Line TOC Analyzer



## Overview

The drive to improve quality and operating efficiencies demands analytical tools that deliver process knowledge and automation. Reliable, real-time data on the production floor has become essential to most quality initiatives.

As a result, many pharmaceutical companies today are working to reduce risks and costs by transitioning Total Organic Carbon (TOC) measurement requirements for pharmaceutical water from laboratory to on-line instruments. There is also a trend to substitute more efficient on-line TOC analyzers for labor-intensive HPLC analysis in cleaning validation applications.

GE Analytical Instruments designed the Sievers 500 RL On-Line TOC Analyzer to deliver science-based risk management capability to the production floor. This was largely achieved by integrating the trusted Sievers laboratory TOC methodology into a reagentless on-line analyzer that delivers the same high level of analytical process capability associated with laboratory analyzers—but without the delay.

The 500 RL Analyzer features automated system protocols, such as validation and system suitability testing, as well as automated recording of production information for Sievers Standards. Data encryption facilitates secure distribution of analytical data for review.

The 500 RL, equipped with a Sievers integrated On-Line Sampling System (iOS\*), provides reagentless on-line TOC analysis for compliance with USP Chapter <643> and EP Chapter 2.2.44 TOC measurement requirements. It also provides USP Chapter <645> conductivity measurement.



## Pharmaceutical Applications

### On-Line Cleaning Validation

One of the pharmaceutical manufacturing industry's most costly, resource-constraining activities is cleaning validation (CV). As the industry focuses on automating more processes critical to improving manufacturing efficiencies, the benefits of real-time, on-line cleaning validation are clear.

The 500 RL monitors TOC and conductivity of the rinse water to determine equipment status during cleaning. To facilitate implementation of on-line CV, GE Analytical Instruments also provides comprehensive documentation via the CV Support Package (CVSP). The 500 RL and CVSP together deliver trusted technology and the applications expertise needed to confidently transition to on-line cleaning validation.

### Real-Time Release of Pharmaceutical Waters

The 500 RL On-Line TOC Analyzer provides continuous, on-line quality assurance for pharmaceutical water release, significantly reducing equipment downtime and eliminating the delays and costs associated with laboratory analyses. The 500 RL also measures USP <645> conductivity, and helps ensure that product waters meet quality requirements during the entire production run.

## Science-Based Risk Management and PAT

To control a process, an analyzer must have less variability than the process itself. Understanding the process capability of your on-line TOC analyzer is critical to the method validation and ultimate use for real-time water release.

The 500 RL On-Line TOC Analyzer was designed to bring the confidence, reliability, and data quality of laboratory TOC analyses to the production floor, facilitating automation through a science-based methodology. Transitioning to on-line TOC analysis for water release and cleaning validation requires a thorough risk assessment. This concept was the genesis of the 500 RL, and all design elements are focused on delivering exceptional process capability.

## Regulatory Compliance

The 500 RL complies with USP <643>, USP <645>, and EP 2.2.44 for TOC and conductivity monitoring for Purified Water (PW) and Water for Injection (WFI). The optional Super iOS, a revolutionary new standards introduction device, greatly simplifies all system protocols, including system suitability and calibration, by fully automating the process, eliminating human variables and reducing labor costs.

## 21 CFR Part 11

Sievers DataGuard\* software, widely used by the pharmaceutical industry, facilitates compliance with 21 CFR Part 11. DataGuard provides an administratively controlled multi-user and multi-level access system, complete audit trail, and electronic

signature management, ensuring secure and traceable data. The new Sievers DataShare\* 500 software allows secure viewing and sharing of the 500 RL's encrypted USB data output, preventing data modification. To facilitate sharing data, DataShare 500 also generates reports, including analysis and protocol data results such as validation or system suitability tests.

## Key Benefits

### Science-Based Design

The Sievers patented membrane conductometric technology is the only on-line TOC measurement technology that demonstrates the level of accuracy and overall process capability needed for compendial water control and release. In a process capability study comparing on-line UPW TOC analyzers, the Sievers 500 RL was the only one demonstrating a meaningful statistical process capability,<sup>1</sup> making it the only on-line TOC analyzer providing confidence that UPW processes are fully protected.

### Sievers TOC Methodology

The Sievers Membrane Conductometric TOC Detection method has proven to be an extremely reliable technique for measuring TOC. The Sievers technology utilizes a gas-permeable membrane that selectively passes only the CO<sub>2</sub> produced from the oxidation of organics. By preventing acids, bases, and halogenated compounds from interfering with the measurement of CO<sub>2</sub> from oxidation, the Membrane Conductometric Method delivers unmatched selectivity, sensitivity, stability, accuracy, and precision.

To see an animated demonstration of the Sievers technology, visit *Products—TOC* at [www.geinstruments.com](http://www.geinstruments.com).

## Applications Versatility

The 500 RL is the only on-line TOC instrument designed with proven laboratory technology for complete applications versatility. This extends the 500 RL's applications range of reliable analytical performance to include high and/or unstable conductivity waters. A maximum sample conductivity specification of 25 µS/cm facilitates extremely reliable performance on all pharmaceutical waters.

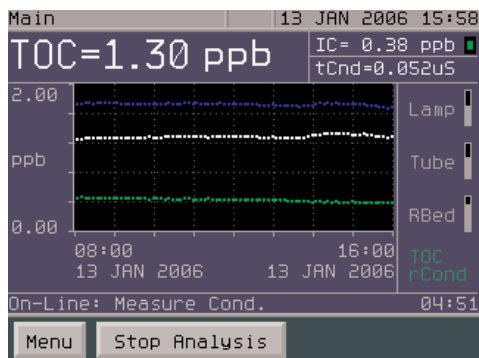
## Automation

The 500 RL is available with a Super iOS that fully automates all validation protocols, including system suitability. Protocol standards come in an innovative vial cartridge which is easily inserted into the Super iOS. Pressing Start on the display menu initiates a protocol, with no further user action required. The 500 RL can also be programmed to restart TOC analysis upon successful completion of most protocols.

## Security

The 500 RL Analyzer protects data and the Analyzer from unauthorized user access. The 500 RL outputs encrypted data files for analysis and system protocol results to a USB Flash memory drive or serial port. The encrypted files can be opened only in the Sievers DataShare\* 500 program and can not be modified. For situations where security is not a concern, non-encrypted data files also may be exported in a .csv format.

The optional Sievers DataGuard\* software facilitates compliance with 21 CFR Part 11 electronic records regulations. DataGuard provides an administratively controlled user-access system supporting multiple users with unique passwords and complete audit trail functionality.



Main Analyzer Display Screen

## USP Chapter <645> Conductivity Measurement and Compliance

The 500 RL Analyzer meets all USP Chapter <645> Stage One regulatory monitoring requirements, reporting raw conductivity, temperature, and temperature compensated conductivity.

## Comprehensive Validation Support

Each 500 RL comes with professional and comprehensive IQ (Installation Qualification) and OQ (Operation Qualification) documents. Optional PQ (Performance Qualification) documentation is also available for a complete validation solution. For cleaning validation applications, an optional CV Support Package provides protocols and documentation to guide users through the process of validating TOC instrumentation for on-line CV.

## Simplicity

The advanced capability of the 500 RL is complemented by user-friendly features that make it easy and fast to install, operate, and maintain. The large, color touch-screen menu provides access to all Analyzer functions. In addition to displaying TOC data, trend graphs, and Analyzer status, the color interface provides real-time status of consumables and prompts the user when semi-annual maintenance is due.

## Easy, Stable Calibration

With 12-month calibration stability and easy screen prompts to perform single-point or multi-point calibration protocols, the 500 RL makes on-site calibration simple and convenient. Super iOS models allow for vial set cartridge insertion, with no further operator action needed.



Sievers Super iOS and Vial Cartridge



Sievers Standard iOS

## DataShare 500

The Sievers DataShare 500 PC-based program allows multiple parties to securely share and review protocol data and reports with signature fields. Data cannot be modified, ensuring data security consistent with 21 CFR Part 11 requirements. On Super iOS models, information embedded in the vial set cartridge is automatically imported into the report.

## Accessories and Options

### Standard iOS and Super iOS

The 500 RL is available in two iOS configurations:

- Single-port standard iOS, for running standards and grab samples
- Four-port Super iOS, for automating all system protocols, including system suitability, verification, and calibration, as well as single standards and grab samples

The Super iOS, together with the Sievers vial set cartridges, provide a robust solution for secure data management. Each vial set cartridge includes an embedded memory chip that transfers data about the standards, including type, concentration, lot number, and expiration, to the Analyzer. This standards information is stored with the protocol results, creating a detailed protocol record and eliminating the need to manually document standards information. For added convenience, the 500 RL with Super iOS can be configured to automatically restart TOC analysis following successful system suitability testing.

### DataGuard for 21 CFR Part 11

Sievers DataGuard software facilitates compliance with 21 CFR Part 11 and electronic records control requirements. DataGuard provides administratively controlled, multi-level and multi-user access, and complete audit trail functionality.

### Sievers Certified Reference Materials

Sievers is the world's leading brand of TOC and conductivity standards. Sievers Certified Reference Materials are available for all validation protocols, including calibration, verification, linearity, and USP system suitability tests. Manufactured in a clean-room environment and using ISO 9001 guidelines, Sievers standards provide the accuracy, stability, and NIST/USP traceability required to provide superior performance in demanding pharmaceutical applications.

## Technical Support and Service

GE Analytical Instruments provides ongoing technical support, as well as on-site installation, maintenance, calibration, and training services that together assure optimal performance from Sievers instruments. For more information, visit [www.geinstruments.com](http://www.geinstruments.com).

## System Specifications<sup>2</sup>

### Total Organic Carbon

Linear Range	0.03 to 2,500 ppb as C
Accuracy	± 5% of measurement
Precision	< 1% RSD or 0.03 ppb as C, whichever is greater
Analysis Modes	On-Line, On-Line Averaged, On-Line Timed
Analysis Time	Continuous mode: 6 minutes Average and timed modes: 0.5, 1, 4, 8, or 24 hours
Ozone Compatibility <sup>3</sup>	Maximum 200 ppb as O <sub>3</sub>
External Flow Rate	Minimum 50 mL/min
Sample Temperature	1° C to 95° C (34° F to 203° F) — withstands short-term steam exposure
Sample Pressure	Up to 100 psig
Interferences	Insensitive to organic heteroatoms
Calibration Stability	Typically stable for 12 months
Display Readout	3 significant digits

### Conductivity

Raw Conductivity Range <sup>4</sup>	0.01 to 35 µS/cm
Conductivity Accuracy <sup>3,4</sup>	± 0.005 µS/cm or ± 1%, whichever is greater
Conductivity Precision	< 0.25% RSD
Maximum Sample Conductivity	25 µS/cm at neutral pH

### Instrument

Power	100–240 ±10% VAC, 50 W, 50/60 Hz
Normal Operating Environment	Intended for indoor use only
Ambient Temperature	10° C to 40° C (50° F to 104° F)
Maximum Relative Humidity	Up to 95%, noncondensing
Maximum Altitude	2,300 m (7,546 ft)
Inputs	One isolated binary input
Outputs	Three isolated 4-20mA outputs, one Serial (RS-232), one USB port, one parallel printer port, and four alarm outputs
Installation/Overvoltage	Category II (protects against transients present in Category II power)
Safety Certifications	UL/cUL, CE
Pollution Degree	2 (normally only non-conductive pollution)
Display	Backlit Quarter-VGA touchscreen display
Dimensions	H: 41.9 cm (16.5 in); W: 48.3 cm (19 in); D: 27.4 cm (10.8 in)
Weight	16.9 kg (37.2 lb)
IP Rating	Environmental IP 23 enclosure

\* Trademark of General Electric Company; may be registered in one or more countries.

<sup>1</sup> Godec, Rick, "A Science-Based On-Line TOC Performance Comparison," GE Analytical Instruments, 2006.

<sup>2</sup> Stated analytical performance is achievable under controlled laboratory conditions that minimize operator and standards errors.

<sup>3</sup> Ozone: 50 ppb continuous, conductivity accuracy ±0.02 µS/cm < 1.0 µS/cm, ±2% >1.0 µS/cm; 200 for 2 hours once/day, conductivity readings not within spec, recovery time to in-spec readings: 2 hours

<sup>4</sup> With optional USP <645> conductivity measurement



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