

Sievers 500 RL

On-Line TOC Analyzer for Pharma Applications

Overview

GE Analytical Instruments designed the Sievers* 500 RL On-Line Total Organic Carbon (TOC) Analyzer to deliver high quality on-line results, consistent with regulatory requirements for both process control and real-time release testing (RTRT). The highly automated Sievers 500 RL, which uses the proven Sievers laboratory TOC methodology, continuously provides exceptional analytical performance at a significantly lower cost than laboratory testing. The Sievers 500 RL offers specific features for pharmaceutical applications, such as the innovative Super iOS* (Integrated On-Line Sampling System) for automating system protocols. The Sievers 500 RL also offers extended calibration stability and the unsurpassed ease of operation found in all Sievers TOC Analyzers.

Key Applications

Regulatory Compliance

The Sievers 500 RL provides on-line TOC analysis for compliance with US Pharmacopeia (USP) <643>, European Pharmacopeia (EP) 2.2.44 Total Organic Carbon, Indian Pharmacopeia (IP) 2.4.30, Chinese Pharmacopeia (CP) Appendix VIII R, and the Japanese Pharmacopeia 16 (JP16) 2.59 monographs for Purified Water and Water for Injection. The robust Sievers 500 RL performance, in conjunction with GE's Quality System Optimization (QSO*) validation program, ensures you can meet all the new regulatory expectations outlined in the FDA Process Validation Guidance document; ASTM E2656; and the ICH Q8, Q9, and Q10 international guidances.

Real-Time Release Testing and Process Control of Pharmaceutical Waters

The Sievers 500 RL provides the low-risk, continuous on-line TOC measurements required to scientifically justify a reduction or elimination of more costly labora-



tory-based sampling processes. The Sievers 500 RL can also provide continuous, on-line quality assurance for pharmaceutical real-time release testing, and can be provided with the critical protocols required for RTRT process validation. The Sievers 500 RL is also an optimum choice if the intended use is focused only on process control. The Sievers 500 RL also measures USP <645> conductivity, and helps ensure that product waters meet quality requirements during the entire production run.

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 and higher quality, the benefits of real-time, on-line cleaning validation are clear.

During cleaning, the Sievers 500 RL monitors TOC and conductivity of process equipment rinse water to determine cleaning status. 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.

Features and Benefits

Science-based Design

GE Analytical Instruments designed the Sievers 500 RL to deliver exceptional analytical process capability. The Sievers membrane conductometric design eliminates false positive and false negative readings to which other technologies are susceptible. Additionally, the Sievers



technology ensures accurate recovery of all classes of organic compounds commonly found in UPW waters. In a process capability study comparing on-line UPW TOC analyzers,¹ the Sievers 500 RL demonstrated the highest degree of suitability for the intended use, making it a clear winner in delivering the highest quality results in pharmaceutical water applications.

Automation

The Sievers 500 RL 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 Sievers 500 RL is available with a Super iOS* (Integrated On-Line Sampling System) that fully automates all validation protocols, including system suitability.

Applications Versatility

The Sievers 500 RL's wide applications range includes high and/or unstable conductivity waters. A maximum sample conductivity specification of 25 $\mu\text{S}/\text{cm}$ facilitates extremely reliable performance on all types of pharmaceutical water.

Conductivity

The Sievers 500 RL Analyzer meets all USP Chapter <645> Stage One regulatory monitoring requirements, reporting raw conductivity, temperature, and temperature-compensated conductivity. Procedures compliant with Chapter <645> enable temperature accuracy verification. The 500 RL also supports conductivity testing in accordance with JP <2.51>.

Security

The 500 RL Analyzer protects data and the Analyzer from unauthorized user access. The 500 RL outputs

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 CO₂ produced from the oxidation of organics. By preventing acids, bases, and halogenated compounds from interfering with the measurement of CO₂ from oxidation, the Membrane Conductometric Method delivers unmatched selectivity, sensitivity, stability, accuracy, and precision.

To see an animated demonstration of the Sievers technology, click on *Videos and Animations* under the Library tab at www.geinstruments.com.

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 cannot be modified.

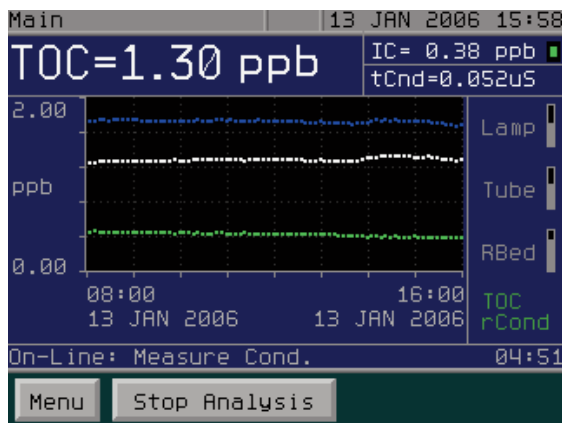
The optional Sievers DataGuard* software facilitates compliance with 21 CFR Part 11 electronic records regulations. DataGuard provides an administratively controlled user-access system supporting multiple users with unique passwords and full audit trail functionality.

Comprehensive Validation Support

Professional and comprehensive IQ (Installation Qualification) and OQ (Operation Qualification) documents are available for the 500 RL. Optional PQ (Performance Qualification) documentation is also available for a complete validation solution. For cleaning validation (CV) 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 Sievers 500 RL is extremely easy to install, operate, and maintain. The large, color touch-screen menu provides access to all 500 RL 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.



Main analyzer display screen

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 once the protocols are started.

Accessories and Options

The Sievers 500 RL is available in two Integrated On-Line Sampling System (iOS) configurations: the Sievers Standard iOS and the Sievers Super iOS.

Sievers Standard iOS

The standard iOS accommodates grab samples and standards used for calibration and system protocols. The single-port standard iOS automatically activates the calibration and verification protocols in the 500 RL's firmware.

Sievers Super iOS

The optional Super iOS, together with the Sievers vial set cartridges, provide a robust solution for secure data management. The Super iOS has four vial ports and uses a unique vial cartridge to automate calibration and pharmaceutical system protocols, eliminating human error and substantially reducing labor costs.

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.

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.



Sievers Super iOS and Vial Cartridge



Sievers Standard iOS

DataGuard

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 leading brand of TOC and conductivity standards sold in the world. Sievers Certified Reference Materials are available for all validation protocols, including calibration, verification, linearity, specificity, robustness, and USP system suitability tests. Manufactured in a stringent cleanroom 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 Services

GE Analytical Instruments provides ongoing technical support and on-site installation, maintenance, calibration, and training services that together assure optimal performance from Sievers analytical instruments. For more information, visit www.geinstruments.com.

System Specifications²

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
pH Range	5.5 to 8.0 in order to meet accuracy specification
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 ³	Maximum 200 ppb as O ₃
External Flow Rate	Minimum 50 mL/min
Sample Temperature	1° C to 95° C (34° F to 203° F)
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 ⁴	0.01 to 35 µS/cm
Conductivity Accuracy ^{3,4}	± 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, four alarm outputs, and one Ethernet port
Installation/Overvoltage	Category II (protects against transients present in Category II power)
Safety Certifications	ETL, 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 (19.0 in); D: 27.4 cm (10.8 in)
Weight	16.9 kg (37.2 lb)
IP Rating	Environmental Enclosure: IP 45

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

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

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

³ 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

⁴ With optional USP <645> conductivity measurement

The Sievers 500 RL TOC Analyzers are protected by one or more of the following US and foreign patents: US 8,003,048; US 5,976,468; US 5,837,203; US 5,443,991; EP 0897530; FR 0897530; GB 0897530; DE 69702516.0-08. Other patents pending.



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