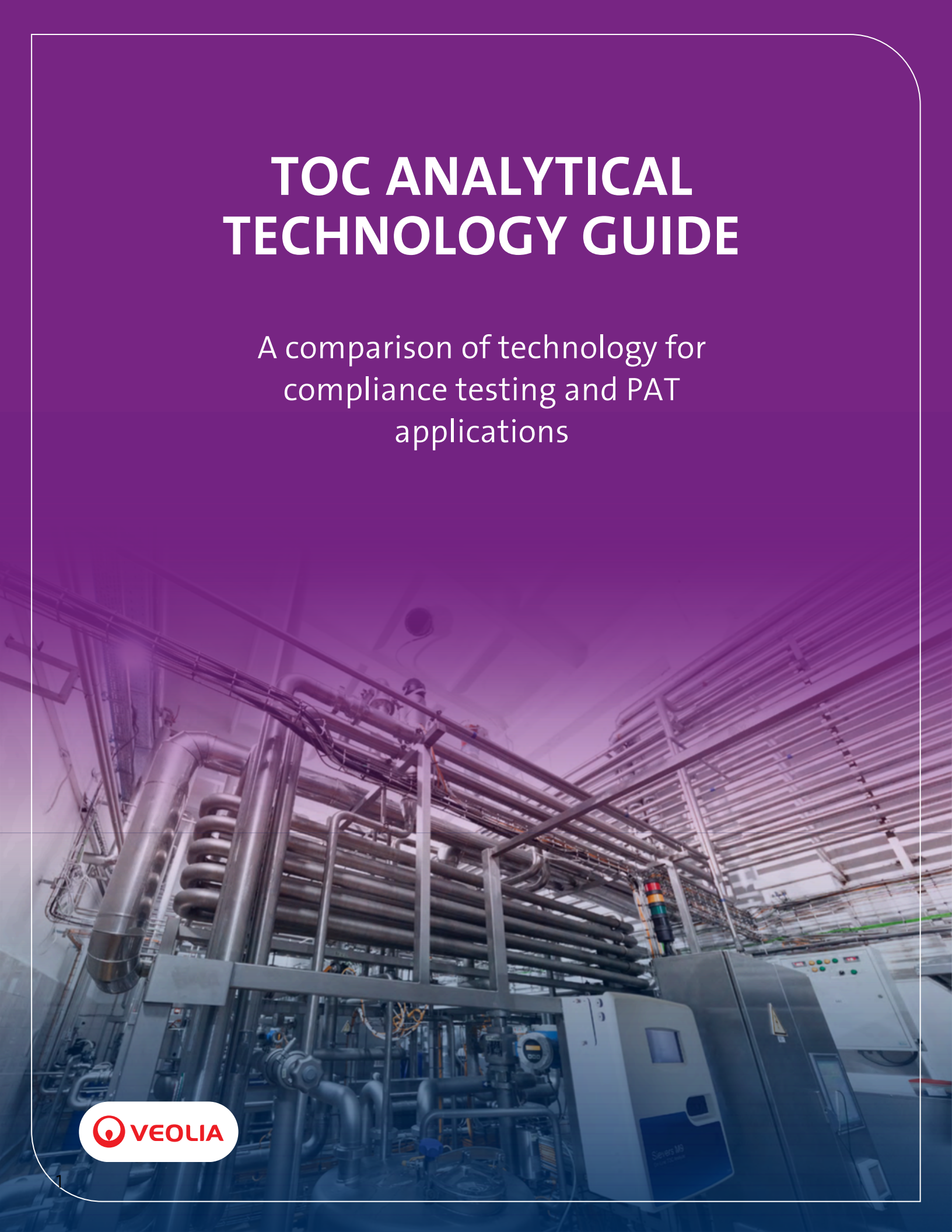
TOC ANALYTICAL TECHNOLOGY GUIDE

A comparison of technology for compliance testing and PAT applications



VEOLIA

What's Your Goal?

Navigating from Basic Compliance to Real-Time Process Understanding with TOC Analysis

Selecting the appropriate total organic carbon (TOC) measurement technology is one of the most critical decisions you will make for your water quality program. When it comes to making critical process decisions based on data, choosing an instrument that supports your intended use can prevent unnecessary out-of-specification investigations, costly downtime, regulatory compliance failures, or even compromised patient safety.

So, how do you determine which technology truly meets your needs?

As the manufacturer of world-leading Sievers* TOC instruments and compendial water testing solutions, Veolia understands the unique challenges life science manufacturers face. Finding the right fit means taking a hard look at your facility's goals. **You need to ask yourself:**

- Are we just trying to meet basic compliance specifications, or are we driving toward advanced process control?
- How much risk are we willing to accept when it comes to false positives or false negatives?
- Are we relying on essential TOC lab testing, or are we ready to implement Process Analytical Technology (PAT) for real-time release testing (RTRT)?
- Are we planning for the future?

At a foundational level: Sensors are typically used to monitor general trends, while analyzers are better suited for advanced process control and compliance.

Your Roadmap to Choosing the Right Technology

In this guide, we'll explore key considerations to achieve a successful water monitoring program:

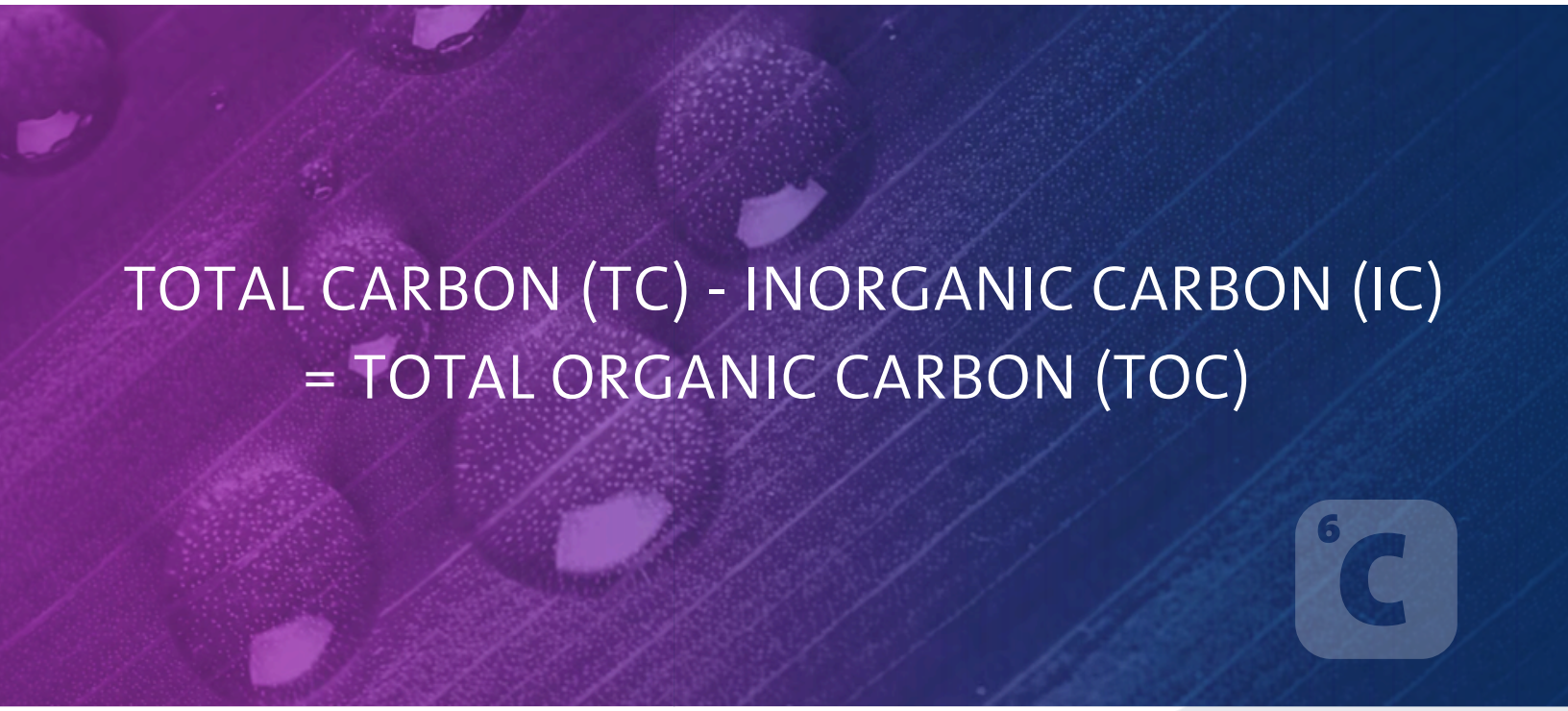
- The science of carbon analysis
- TOC sensor vs. analyzer comparison
- Navigating risk and intended use
- Real-world challenge compounds
- The path to PAT and RTRT
- Technology assessment quiz!

The Science of TOC Measurement

Converting Carbon to Measurable CO_2

In order to measure carbon accurately, it must first be converted to CO_2. This is achieved through oxidation, often via the addition of reagents and/or UV irradiation.

Once converted, the amount of total organic carbon (TOC) is determined by a simple calculation:



TC (Total Carbon):

All carbon present in a sample, including both organic and inorganic forms

IC (Inorganic Carbon):

Carbon present in inorganic compounds (such as CO_2 , HCO_3^-, and CO_3^{2-})

TOC (Total Organic Carbon):

The amount of carbon remaining after inorganic carbon has been measured and subtracted from total carbon

Summary: Technology Comparison and Fit

TOC sensors and analyzers serve important but different roles in today's pharmaceutical water applications.

	TOC Sensors *for monitoring*	TOC Analyzers *for compliance & process control*
TECHNOLOGY	**DIRECT CONDUCTIVITY DETECTION** Measures sample conductivity pre-and post-oxidation but without discriminating between carbon and other ions	**MEMBRANE CONDUCTOMETRIC DETECTION** Uses a selectively permeable membrane to physically separate CO_2 from interfering ions, ensuring accurate measurements
USP <643> COMPLIANCE	Limited, cannot discriminate IC	Compliant, independent measurement to accurately discriminate between IC and TOC
RISK OF INTERFERENCE	High (false positives/negatives)	Low (mitigated by membrane)
VALIDATION SUPPORT	IQ / OQ	IQ / OQ/ PQ
SUITABILITY AS PROCESS ANALYTICAL TECHNOLOGY (PAT)	Not compatible (high risk)	Essential, best fit Supports RTRT
INTENDED USE	General monitoring & trending	Process control & RTRT • Criticaldecisions • Troubleshooting • PAT

The Limitation: Inferred Carbon Analysis
Lacks a separation mechanism, leading to false negatives and false positives, influenced by salts, acids, cleaning agents, etc.

The Risk:
- Over-reporting: TOC triggers expensive, time-consuming out-of-specification (OOS) investigations and unnecessary downtime
- Under-reporting: Interferences can mask actual contamination, directly compromising product quality

The Advantage: True Carbon Measurement
Provides accurate, quantitative results by measuring only carbon-sourced CO_2

The Result:
- Highly accurate data allows for automated product release (RTRT) and immediate root cause analysis during excursions
- Confident decision-making and compliance

Compliance Check: USP <643>

USP <643> requires the ability to discriminate between CO_2 generated from inorganic carbon (IC) and CO_2 generated from the oxidation of organic molecules, or TOC.

Sensors lack a way to discriminate between these carbon sources
Analyzers accurately and precisely measure both IC and TOC to ensure compliance

Where TOC Sensors Struggle

The Real-World Risk of Interfering Compounds

TOC sensors measure a change inconductivitypre- and post-oxidation without separating out interfering ions. When your water system encounters certain types of compounds, this lack of discrimination puts you at direct risk of reporting TOC false positives and TOC false negatives.

What Makes a Compound "Challenging"?

Challenging compounds typically fallin to a few categories that disrupt the direct conductivity measurement process:

- **Difficult-to-Oxidize Structures:** Incomplete oxidation of compounds can lead to inaccurate carbon measurements due to ionic species
- **Conductivity Interferents:** High-salt compounds and basic buffer components can skew conductivity readings
- **Common Pharmaceutical Contaminants:** Large complex formulations, alcohols used as solvents, and biologics (such as microbes)

The Cost of TOC False Positives (Over-Reporting)

You chase ghosts.

Falsely elevated TOC readings lead to unnecessary OOS investigations, maintenance, and lost product. These are time-consuming and expensive, and when the root cause is unknown, it can be hard to defend during an audit.

The Danger of TOC False Negatives (Under-Reporting)

You miss the threat.

Incomplete oxidation or interference masks actual contamination, compromising product quality and, ultimately, patient safety.

Consider this: QC and facility managers don't want to be running down the hall trying to solve a problem they don't have, or be caught off guard by problems they didn't even know they had.

Real-World Application

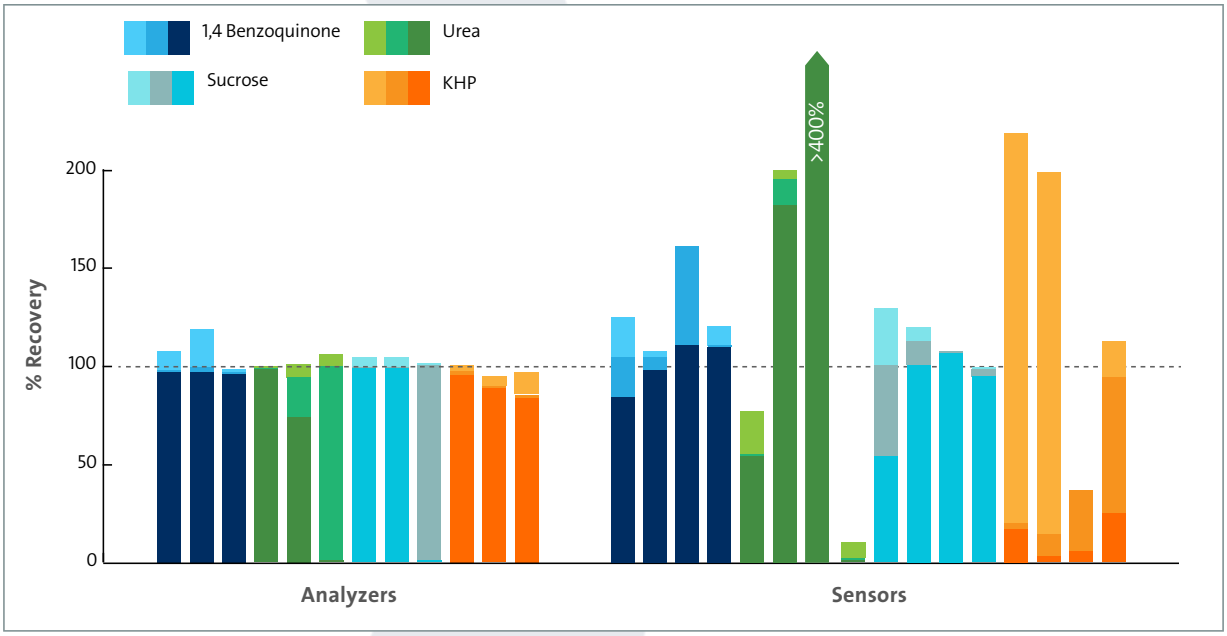
Comparative Evaluation of Technologies

The figure below summarizes multiple linearity studies comparing three TOC analyzers against four common TOC sensors across 100 ppb, 500 ppb, and 2000 ppb dilutions. Samples were run mimicking real-world operations (not system protocols) to demonstrate how differences in technology impact the recovery of various organic compounds.

What the study demonstrated:

- **Over- and Under-Reporting of Sensors:** TOC sensors exhibited falsely elevated recoveries for chlorine-, sulfur-, and nitrogen-containing organics, and consistently low recovery of organic acids.
- **System Suitability Challenges:** TOC sensors demonstrated high sensitivity to trace non-organic ions, complicating standards preparation and system suitability testing.
- **The Advantage and Consistency of Analyzers:** By utilizing membrane conductometric technology to prevent measurement interferences, TOC analyzers successfully achieved approximately 100% recovery across all tested compounds and concentrations.

Recovery of Compounds in UPW Systems (100, 500 and 2000 ppb Dilutions)



Note: Data represents average performance across multiple leading manufacturers, including Veolia's sensor technologies. The variance highlights the limitations of the detection method itself, not specific instruments.

Modeled vs. True Measurement - The Bottom Line

Because direct conductivity sensors do not physically isolate CO_2, the reported TOC value is a modeled interpretation of conductivity behavior. If your sample chemistry is stable and well understood, this provides useful trending information. But if the ionic composition or oxidation behavior of your sample varies, the sensor's underlying assumptions break down. The ability to accurately detect anomalies is vital to instrument reliability.

SENSORS ARE TYPICALLY USED TO MONITOR, WHILE ANALYZERS ARE BETTER SUITED TO MANAGE A PROCESS.

Monitor versus manage

If the intended use of the TOC instrument is for regulatory reporting, managing an important process control variable, real-time release, or other critical-to-quality product attributes, **then accurate, quantitative, audit-ready data is essential**. In those situations, a TOC analyzer is needed to **ensure compliance and process control.**

Real-Time Release Testing

Traditional end-product testing forces facilities to wait for offline lab results before releasing water into production. But as the FDA's Process Analytical Technology (PAT) framework clearly states, quality cannot simply be tested into products; it must be built-in by design. Real-Time Release Testing (RTRT) changes the paradigm, allowing you to evaluate and ensure acceptable water quality based on **continuous, scientific risk-based process monitoring.**

The Speed vs. Accuracy Trap

Some manufacturers promote online TOC sensors for PAT applications simply because they offer fast, continuous readings. However, the ultimate goal of PAT is robust process understanding and control. As we have seen, sensors rely on inferred, modeled interpretations of conductivity. If your real-time data is skewed by false positives or complex chemistry, "fast" data becomes a compliance liability rather than a tool for true process understanding.

Why TOC Analyzers are Essential for RTRT

To successfully implement PAT and confidently release water in real time, you need an instrument that delivers quantitative, defensible process understanding and **automatic alignment with data integrity principles.** Here is why TOC analyzers set the standard:

- **Comprehensive Data for Continuous Quality Assurance and Root Cause Analysis:** Analyzers provide simultaneous, quantitative data for TOC, inorganic carbon (IC), and conductivity – giving you the multi-attribute process understanding necessary to demonstrate control and mitigate risk.

- **Seamless Regulatory Alignment Using a Risk-Based Scientific Approach:** Moving to RTRT requires a lifecycle approach that goes beyond basic method suitability. Analyzers generate the proven, quantitative data required for rigorous instrument qualification **(IQ/OQ/PQ)** and comprehensive regulatory alignment:

    - **FDA PAT Guidance & ASTM E2656-16:** Standard best practice guidances for implementation of PAT technologies to gain the process understanding necessary for transition to RTRT based on validated quantitative online TOC data
    - **USP Monographs:** Robust method validation and compliance with USP <1225> and USP <1231>
    - **Global Best Practices:** Stringent contamination control requirements, such as Annex 1 for sterile manufacturing
    - **Data Integrity:** Compliance with ALCOA+ and 21 CFR Part 11, managing TOC, IC, and conductivity data for real-time insights and audit readiness

- **Like-for-Like Method Transfer:** Because Sievers analyzers use the same robust technology both in the lab and online, like-for-like method transfer is seamless. You preserve functional equivalence while upgrading to continuous real-time control.

The Bottom Line: Real-time release isn't just about getting defendable data faster; it is about having data you can trust to make critical quality decisions and demonstrate true process validation with every batch.

Contamination Control

Real-Time Data for Continuous Control and Root Cause Analysis

Total organic carbon and conductivity testing are required for pharmaceutical-grade water systems under USP <643> and USP <645>. When monitored in real time with online technology, these metrics provide value far beyond basic compliance.

By utilizing simultaneous quantitative data for TOC, inorganic carbon (IC), and conductivity, you have powerful, trending data to enhance process understanding. When combined with a statistical analysis of process capability, this allows you to set highly accurate alert and action levels, identify root causes during an excursion, mitigate risk, and demonstratetrue systemcontrol to an auditor.

Identifying Contamination Sources with Trending Data

When a water system excursion occurs, utility uptime depends on how quickly you can identify the root cause. Because sensors generate inferred IC data and are prone to interference which may over- or under-report TOC, they obscure the true source of contamination. To rapidly troubleshoot your system, you need the three distinct data streams only an analyzer provides. Consider these scenarios for troubleshooting:

Scenario 1: Organic Contamination

TOC ↑ Conductivity ↑ IC →

Indicates degrading gaskets or presence of sugars.

Risk when using sensors:
Without direct measurement of IC, sensor data may point to a system leak and delay the identification of a degrading gasket.

What is Your Water Telling You?

Scenario 2: Non-Carbon Contamination

TOC → Conductivity ↑ IC →

Indicates leaching or cleaning residues (NaOH, KCl).

Risk when using sensors:
Changes in conductivity caused by ionic speciescanbe misinterpreted by sensorsas IC unless IC is measured directly.

The Importance of Three Distinct Data Streams

How would you identify your contamination source in Scenario 2 vs Scenario 3 **without inorganic carbon data?**

Scenario 3: Atmospheric Leak

TOC → Conductivity ↑ IC ↑

Indicates CO_2 contamination or a system leak.

Risk when using sensors:
Because a sensor cannoteffectively separate IC from TOC, it may falselyregister this CO_2 spike as an organic contamination event, triggering a costly, unnecessary investigation.

The Limitations of Offline Grab Sampling

Risk:

- Environmental contamination
- Technician sample handling
- Possibility for vial contamination

Time Delay:

- Manual sampling and transport
- Must wait for lab results
- Lack of real-time process control

TOC sensors do not provide reliable IC measurements, making it difficult to identify contamination sources without additional testing.

The Crucial Role of Performance Qualification (PQ)

PQ provides the validated process understanding and historical data necessary to establish reliable PAT models and real-time release strategies. It is the evidence required to enable immediate product disposition without relying on traditional end-product testing alone.

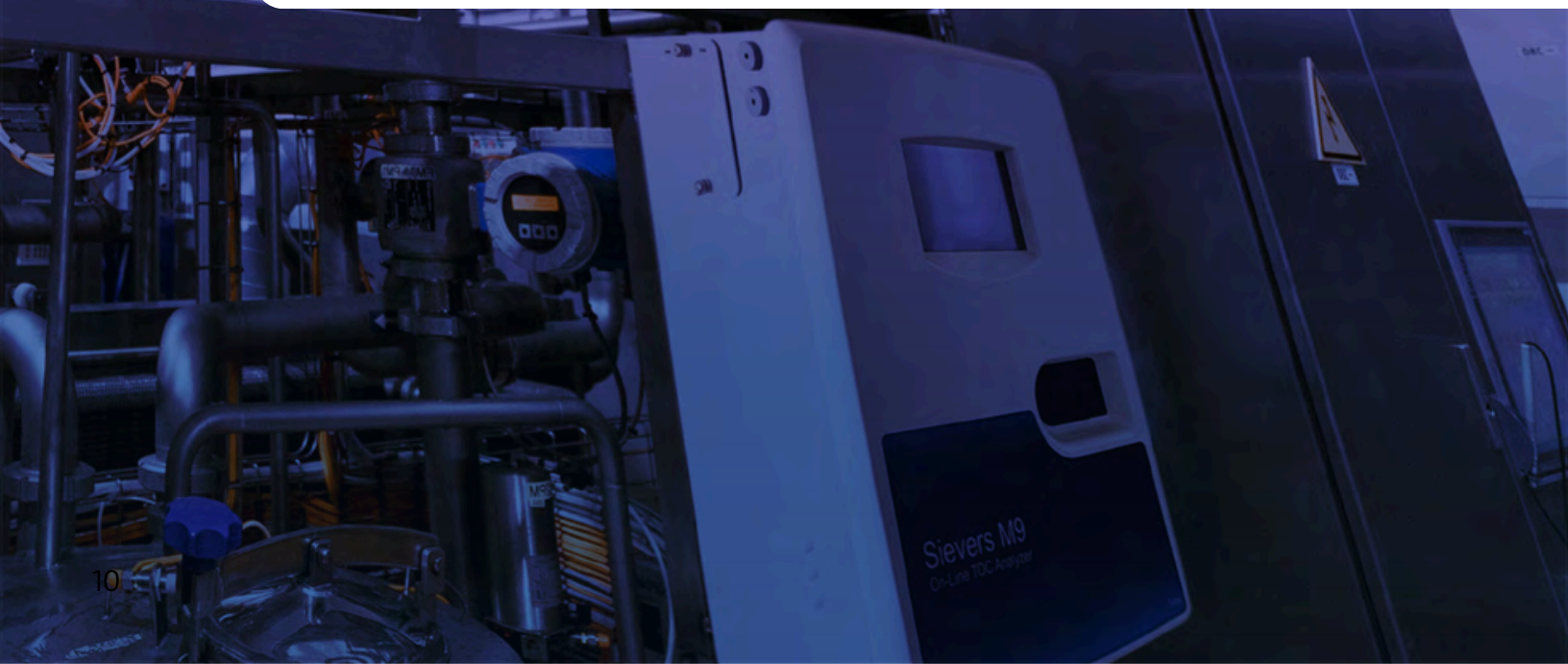
However, not all technologies are equipped for this critical step. While TOC sensors often lack standardized PQ protocols due to their technological gaps, TOC analyzers utilize comprehensive PQ documentation for quantitative analysis that enhances compendial method compliance and instrument qualification, while satisfying validation requirements.

Like-for-Like Technology: Ensuring a Smooth Transition to Real-Time Release Testing

Not every facility is ready to implement full Process Analytical Technology (PAT) and real-time release today. But the technology you choose for your lab right now dictates how difficult that transition will be tomorrow.

By selecting a Sievers TOC Analyzer for your lab, you gain an advantage through like-for-like technology that can help you automate your process later. Because the same established, robust measurement methods are used in both Sievers lab and online instruments, method transfer is seamless.

This approach creates a streamlined implementation pathway, accelerates regulatory acceptance, and preserves your options for continuous monitoring and RTRT whenever your organization is ready to advance.



How Challenging is Your Water Application?

Self-Assessment

Take this quick assessment to determine which technology is best suited to support your facility in managing risk and compliance.

Process & Control

Y N 1. Are you using TOC data to control Critical Process Parameters (CPPs) rather than just monitoring general trends?

Y N 2. Are you implementing (or planning to implement) Process Analytical Technology (PAT) or Real-Time Release Testing (RTRT)?

Y N 3. Does your facility require continuous, real-time data collection every few minutes to actively demonstrate process control?

Troubleshooting & Risk

Y N 4. Is high-purity water a critical ingredient in your final manufactured product?

Y N 5. Would a false positive (over-reporting) or false negative (under-reporting) of TOC create significant product safety or compliance risks for your facility?

Y N 6. When troubleshooting an excursion, do you rely on having simultaneous, quantitative data for inorganic carbon (IC) and conductivity?

Regulatory Compliance

Y N 7. Must you strictly differentiate between organic and inorganic carbon sources, as specified in USP <643>?

Y N 8. Are 21 CFR Part 11 and ALCOA+ data integrity guidelines a strict requirement for your electronic quality records?

Y N 9. Are your measurements used to document official compliance with global pharmacopoeia standards (e.g., USP <643>/<645>, EP 2.2.44) for Purified Water or WFI?

COUNT YOUR **YES ANSWERS** TO DETERMINE YOUR TECHNOLOGY FIT

0-2 Yes Answers: Fine as-is

3-5 Yes Answers: Moderate risk, TOC Analyzer is recommended
Consider the cumulative impact of measurement accuracy on your facility and your process. When transitioning toward process control, an analyzer provides the necessary defensible data to mitigate your risk.

6-9 Yes Answers: High risk, TOC Analyzer is critical
Your application demands precision. Accurate TOC measurements are essential to support real-time release, satisfy auditors, and prevent costly compliance failures.

Conclusion

What is Your Risk Tolerance?

If your goal is simple, high-level trending, a TOC sensor may suffice. But if you rely on data for process control, audits, or real-time release, sensors introduce severe business risks:

- **The Danger of False Negatives(Under-Reporting):** Masking true contamination threatens product safety and can lead to compliance failures
- **The Cost of False Positives (Over-Reporting):** Chasing "ghost" contamination can result in expensive, unnecessary Out-of-Specification (OOS) investigations that reduce utility uptime

ALCOA+ Reality Check

Software cannot fix bad data. Many TOC sensor manufacturers heavily promote their 21 CFR Part 11-compliant software, but software alone does not guarantee data integrity. If your sensor's underlying detection method struggles with complex chemistry and interference, it will generate flawed data.

True ALCOA+ data integrity begins at the point of detection. By physically separating carbon from interfering ions using membrane conductometric technology, Sievers TOC Analyzers deliver truly accurate, quantitative, and defensible measurements.

In a highly regulated environment, your risk tolerance should be reduced. Choosing a Sievers TOC Analyzer ensures that the data you use to make critical quality decisions is data you can trust.

While every facility must balance its own unique operational demands, true process control doesn't leave room for measurement uncertainty. In pharmaceutical water monitoring, less risk isn't just better - it's essential.

TOC & Conductivity Monitoring with Sievers Instruments

Sievers TOC Analyzers deliver the quantitative data and process understanding required for PAT and real-time release.

Sievers M500 Online

TOC and Conductivity for Real-Time Release Testing

Use

Ultrapure Water
Water for Injection

Time to results

0.03 ppb - 2.5 ppm TOC

Time to results

Results in 3 minutes for continuous online measurements

Sievers M9 Analyzer Portfolio

Compliant, Simultaneous TOC and Conductivity

LAB WITH AUTOSAMPLER

PORTABLE

ONLINE

Use

Ultrapure Water
Water for Injection

Cleaning Validation
In Process

Range

0.03 ppb - 50 ppm TOC

Time to results

Results in 2 minutes
(4 seconds with the optional Turbo Mode)

SIEVERS TOC ANALYZERS

Designed For high-risk applications, process control & RTRT. Choose Sievers TOC Analyzers for rigorous process control and ALCOA+ compliant, multi-attribute (TOC/IC/Cond) data.

SIEVERS CHECKPOINT PORTABLE TOC SENSOR

For Lower-Risk General Trending

Portable and light weight, the Sievers Check Point TOC sensor allows superior flexibility when measuring low-level TOC. This sensor is a powerful tool for rapid diagnostic sampling and troubleshooting in pharmaceutical applications and across various industries.

Resourcing the world

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