e-book

Total Organic Carbon for cleaning validation programs;

laboratory, online & at-line analysis

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introduction

Cleaning validation programs are essential to cGMP manufacturing to ensure product quality and patient safety. Total organic carbon (TOC) testing is a compliant method to demonstrate cleanliness of equipment. Unlike specific methods, TOC gives a comprehensive understanding of cleanliness while gaining process efficiencies. Whether you are new to cleaning validation or a seasoned TOC user, this e-book will provide all levels a wide-ranging understanding of the what, how, and why of TOC for cleaning validation.

analytical methods in cleaning validation

the challenge

A typical cleaning validation (CV) program consists of three phases:

1) Design

2) Validation

3) Continued Verification

A key industry challenge is how to select the most appropriate analytical method(s) for evaluating known and potential residues throughout the different phases of a CV program.

For example, in early design-phase work, adequate information on the cleanability of the worst-case compounds or their degradants may not be known. This may create challenges in developing product-specific analytical methods as these tests assume that all potential interferences are known. Similarly, in the validation phase, product-specific analytical methods may be less useful as common residuals may include uncharacterized degradants or more difficult to clean compounds rather than a target active pharmaceutical ingredient (API). Lastly in the continued verification phase, manufacturing concerns including product change-over, equipment turnover, cost, and a desire for continuous or automated monitoring may influence the methods used.

cleaning process method selection

In many situations, cleaning process-specific methods such as total organic carbon (TOC) analysis (in contrast to product-specific methods) may give a very accurate picture of the overall effectiveness of the cleaning process at every phase of a cleaning validation program. A key point is that selection of one or more methods will depend on the nature of the residue as it exists after the cleaning process. If an active ingredient is not degraded or dissolved during a validated cleaning process and all interferents are well understood, then more product-specific methods including HPLC, UV/Vis, or ELISA may be appropriate.[1,2]

common product-specific analytical methods

The following product-specific analytical methods have historically been used in cleaning applications. All are designed to determine if a specific compound is present in its original form.

High Performance Liquid Chromatography (HPLC)

HPLC involves the separation of a unique compound from a matrix by chromatography, followed by measurement of the compound with a UV or other detector.

- Advantages: Ability to identify the presence of a particular residual compound, may provide data on the nature of a cleaning failure
- Challenges: Assumes compounds have not degraded in the cleaning process, that all potential interfering or residual compounds are fully understood, and may require extensive method development

Enzyme Linked Immunosorbent Assay (ELISA)

ELISA is an antigen or antibody type reaction using specific chemicals and standards. If the specific protein is intact and present in the test solution it will bind to the enzyme. This binding is then detected. However, if the protein is denatured but still present in the solution, the ELISA test will not detect the denatured content. ELISA has many of the same advantages and challenges as HPLC, but applied to biopharmaceutical manufacturing.

Ultraviolet/Visible Spectrophotometry (UV/Vis)

UV/Vis involves the measurement or absorbance of a specified wavelength of light by a solvent solution of the residue.

- Advantages: Simplicity, does not require separation of a residual from a matrix
- Challenges: Not applicable to all compounds, potential interferences from other light adsorbing compounds

cleaning validation from HPLC to TOC: three factors to consider

Total Organic Carbon (TOC) analysis is often preferred over traditional, product-specific methods for cleaning validation due to its speed, simplicity, and ability to enhance process understanding.

HPLC vs. TOC

TOC analysis offers several benefits over HPLC, including:

- Better process understanding
- Faster sample analysis
- Simpler method development
- Greater productivity
- Opportunity for at-line and online efficiency gains
- Lower operating costs

Here are 3 factors to consider to help you get started with TOC:

1 Cleaning process/sample compatibility

Does the existing cleaning cycle use a final aqueous rinse?

Understanding your current process will help determine if an aqueous final rinse is possible.

2 Cleaning limit acceptance criteria

Is the acceptance criteria limit within the linear dynamic range of the TOC analyzer?

Convert existing specific product limits to TOC limits using the percent carbon in the chemical formula to determine if they are within the range of the instrument.

3 Product recovery/solubility

Are your compounds soluble enough for TOC?

Even traditionally insoluble or difficult-to-solubilize compounds such as ibuprofen, starch, and lidocaine can often be recovered by TOC with little or no pretreatment.

TOC may be a great match for your CV program.

To learn more, visit **www.suezwatertechnologies.com/applications/cleaning-validation**

common process-specific analytical methods

The following process specific (or non-product specific) methods are commonly used in cleaning applications.

Total Organic Carbon (TOC)

TOC methods oxidize all organic residues and measure the carbon dioxide produced.

- Advantages: Sensitive to all aqueous organic compounds including degradants or unexpected compounds, simple method development (single method), applicable to all phases of CV
- Challenges: Excellent for identifying a CV process failure but investigations may require complimentary methods, compounds must be aqueous

Conductivity

Conductivity is used to detect ionic substances in cleaning rinse samples, most commonly used to detect traces of acidic or basic cleaning agents during a final rinse.

- Advantages: Easy to automate (online), highly sensitive to ionic residues, simple method development (single method)
- Challenges: Only applicable to a subset of compounds (cleaning agents or ionic APIs), for use with rinse samples only

other analytical methods

In addition to product- and process- specific methods commonly used in cleaning validation programs, other analytical methods for consideration may include:

- Visual inspection
- Bioburden or endotoxin for detection of biological residuals
- Ion mobility spectrometry for quick analysis of specific target compounds
- pH to detect acidic or basic cleaning agents
- Infrared methods (NIR/FTIR) used in-situ to identify residues on surfaces

discussion

It is essential to any cleaning validation program that analytical methods are selected appropriately for their intended use. Analytical methods should be able to adequately determine that a validated cleaning process was completed as designed, thereby minimizing the risk of product contamination.

In an ideal world, the best analytical method for a given phase (design, validation, verification) could be chosen. However, in the real world of cleaning validation, selection of analytical methods may be limited by practical considerations based on the cleaning process and the intended use of the method. Therefore, it is more important for the analytical method to be adequate or suitable rather than the "perceived" best method for the intended purpose.[2]

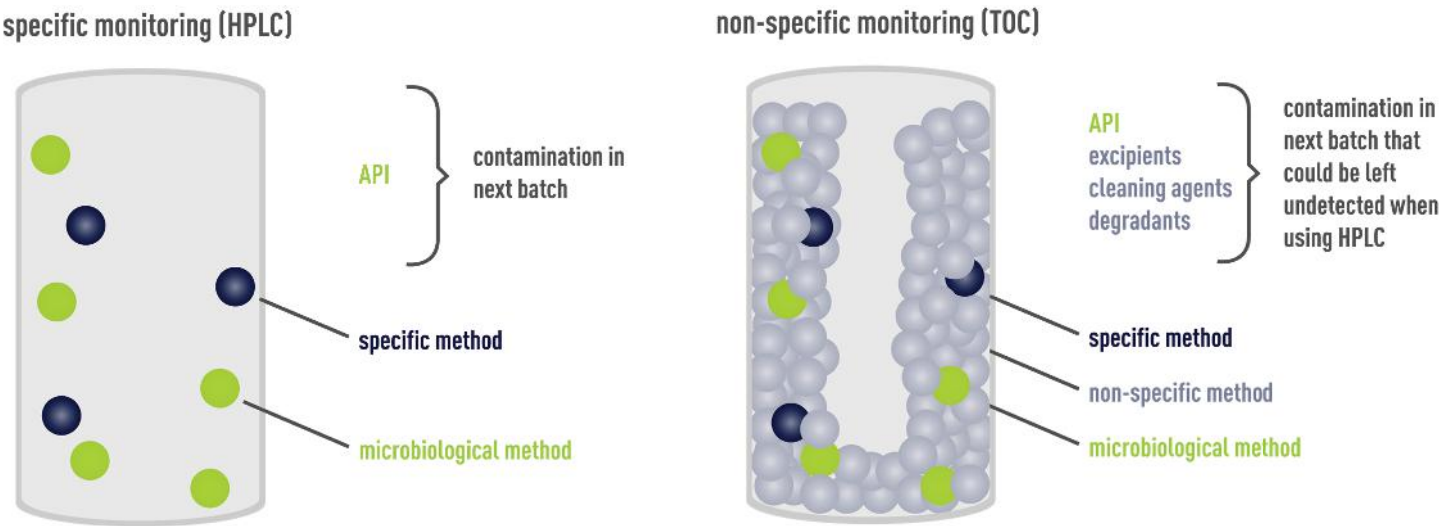
References

1. Technical Report No. 29 (Revised 2012) Points to Consider for Cleaning Validation. PDA, 2012, https://store.pda.org/tableofcontents/tr2912_toc.pdf

2. Technical Report No. 49 Points to Consider for Biotechnology Cleaning Validation. PDA, 2010, https://store.pda.org/tableofcontents/tr49_toc.pdf

comparison of specific and non-specific analytical methods

Specific methods of cleaning validation are intended to detect a single compound of interest such as an active pharmaceutical ingredient (API). This gives a very limited understanding of the cleanliness of a piece of equipment. Degradants, cleaning agents, excipients, or other sources of contamination could be present and left undetected by a specific method of monitoring. With total organic carbon (TOC) and conductivity monitoring, a comprehensive assessment of cleanliness can be used to release equipment confidently.



calculating maximum allowable carryover (MAC) for cleaning validation

The United States Food and Drug Administration (FDA) released guidance for current Good Manufacturing Process (cGMP) validation in January 2011.[1] Within that guidance, the traditional approach of process validation has been replaced with a life cycle approach as the best practice recommendation. The life cycle approach is broken into three stages: Design, Qualification, and Verification. The three stages are no longer viewed as static steps but rather dynamic stages to be constantly reviewed and updated during the lifetime of the process. This new direction for process validation applies directly to cleaning validation (CV) as well.

The traditional objective of any pharmaceutical manufacturing cleaning process is to remove or reduce the Active Pharmaceutical Ingredient (API), degradants, excipients, and cleaning agent residues. This is important to ensure product integrity and patient safety.

With the new life cycle approach to process validation, the traditional practice of measuring a single API with a specific method does not elicit the necessary process understanding and, therefore, is no longer compliant with US FDA best practice guidance. As a nonspecific method, Total Organic Carbon (TOC) analysis measures both product and process related residues as a function of their carbon containing properties. TOC analysis provides efficient feedback necessary to continuously evaluate the validated state of the cleaning process and, therefore, is compliant with FDA best practice guidance.

A key question for any cleaning validation process is how to establish practical, achievable, verifiable, and scientifically defensible acceptance criteria limits. This chapter presents a framework for how to establish acceptance criteria limits using TOC to comply with FDA best practice guidance for the life cycle approach to cleaning validation.

know your process

One of the many challenges to implementing a cleaning validation process is that each manufacturing process is unique. Raw materials, process flow diagrams, manufacturing procedures, run rates, Minimum Batch Size (MBS), and order of operations are a just a few of the factors that can affect cleaning processes. Additionally, how each manufacturer cleans and how each manufacturer measures also present unique challenges to implementing a cleaning validation process. These factors are not addressed in this application brief but must be understood prior to calculating MAC.

product change over

The need for determining MAC for a given product stems from the practice of product change over in a production facility. Product change over, just as it sounds, occurs when a vessel is emptied of one product (Product A) and then refilled with a different product (Product B), as shown in Figure 1. The MAC value is how much of Product A can safely be present in Product B without any danger to the patient.

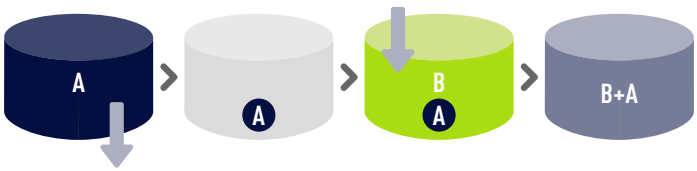


Figure 1. Product change over from A to B illustrating carryover of A into B.

reference values in developing acceptance criteria

MAC calculations start by identifying clinical reference values for each product. These may include, but are not limited to, Therapeutic Daily Dose (TDD), Acceptable Daily Intake (ADI), Lethal Dose for 50% of population (LD50), or Permitted Daily Exposure (PDE). Clinical reference values may be found in literature or online, including PubChem DSSTox FDA Maximum Daily Dose Database (DSSTox FDAMDD).[2] Regardless of the citation source for starting reference values, they must be scientifically defensible. Starting reference values in this application brief originate from DSSTox FDAMDD.

MAC from TDD

When determining MAC from TDD, the current product in the tank (Product A) and the next product in the tank (Product B) must be known (see Figure 1). The known identity of both products allows identification of a defensible starting clinical reference value. Depending on what types of compounds Product A and B are, a different Safety Factor (SF) in the calculation is used based on the risk assessment of those compounds.[3] A typical safety factor value is 1000.[3]

$$MAC_A = \frac{TDD_A \; x \; MBS_B}{SF \; x \; TDD_B}$$

MAC from LD_{50}

As with TDD, when determining MAC from LD50, the current product in the tank (Product A) and the next product in the tank (Product B) must be known (see Figure 1). Next, calculate the No Observed Effect Limit (NOEL) using the LD_{50} reference value for Product A. Then, calculate MAC from the derived NOEL value. Please note that the denominator value of 2000 in the NOEL equation is an empirical constant referenced in literature.[3]

$$NOEL_A = \frac{LD_{50\ of\ A} \; x \; 70\ kg\ (avg.patient\ mass)}{2000}$$

$$MAC_A = \frac{NOEL_A \; x \; MBS_B}{SF \; x \; TDD_B}$$

MAC to product limit

A MAC value alone is not sufficient to release equipment for use. Once MAC has been determined, the value must be converted into an actual product limit (in ppm). The product limit accounts for the sampling method with the MAC value.

Two common sampling methods are:

1. collecting a swab sample from inside the tank
2. collecting a rinse grab sample

Product Limit from Swabbing

If sampling involves swabbing a specified area in the tank, the target value may be calculated using the MAC value, assuming an even, homogenous API deposition throughout the active surface area.

$$Product\ Limit\ \left(\frac{mg}{dm^2}\right) = \frac{MAC(mg)}{Active\ Surface\ Area\ (dm^2)}$$

Product Limit from Rinse

If sampling involves collecting a final rinsate from the tank, the MAC value is converted into a concentration (mg/L) based on final rinse volume.

$$Product\ Limit\ \left(\frac{mg}{L}\right) = \frac{MAC(mg)}{Total\ Rinse\ Volume\ (L)}$$

product limit to TOC limit

Specific product limits are not directly transferrable to a TOC method. The specific product limit, depending on the sampling method, can be converted to a TOC limit by multiplying by relative mass percentage of carbon from the chemical formula of the product.

When a specific method limit has been previously calculated, converting from the specific cleaning validation method, such as HPLC, to a nonspecific method, such as TOC, can be achieved using the percentage carbon in the chemical formula. For example, if a specific API limit for HPLC is established at 10 ppm and the percentage carbon is 50%, the TOC limit would be 5 ppm.

example using TDD

In this example, Product A is Epinephrine and Product B is Diazepam. The clinical reference values are as follows[2]:

$$TDD_A(Epinephrine) = 0.0167\ \frac{mg}{kg\ bw}$$

$$TDD_B(Diazepam) = 0.667\ \frac{mg}{kg\ bw}$$

The example process information on Minimum Batch Size (MBS), safety factor, and average patient mass (kg body weight) are as follows:

$$Avg.Patient\ Mass = 70\ kg\ bw$$

$$MBS_B(Diazepam) = 7.0\ x10^7 mg$$

$$SF = 1000$$

With this information, the MAC value of Epinephrine into Diazepam (MACA in B) can be calculated.

$$MAC_{A\ in\ B} = \frac{\left(0.0167\ \frac{mg}{kg\ bw}\ x\ 70\ kg\ bw\right) x\ (7x10^7 mg)}{1000\ x\ (0.667\ \frac{mg}{kg\ bw}\ x\ 70\ kg\ bw)}$$
$$= 1752\ \text{mg}$$

The MAC value must now be converted to a product limit by considering the sampling method. In this example, the method is swabbing a 1 dm^2 area inside a tank. The active surface area of the tank is 80% of the total based on the fill level of the tank.

$$Active\ Surface\ Area = 1500\ dm^2\ x\ 0.8$$
$$= 1200\ dm^2$$
$$Epinephrine\ Product\ Limit = \frac{1752\ mg}{1200\ dm^2}$$
$$= 1.46\ \frac{mg}{dm^2}$$

The TOC vial volume of 40 mL is also known. Since the sampling method is swabbing, the swab will be broken off in the vial; therefore, the final product limit concentration for Epinephrine is as follows:

$$Vial\ Volume = 0.040\ L$$

$$Epinephrine\ Product\ Limit = \frac{1.46\ mg}{0.040\ L}$$
$$= 36.5\ ppm$$

With the product limit established, the TOC limit can be determined by the percent carbon in the chemical formula for Epinephrine, $C_9H_{13}NO_3$.

$$\%\ Carbon\ (Epinephrine) = \frac{9\ x\ 12.010\ \frac{g}{mol}}{183.207\ \frac{g}{mol}}\ x\ 100$$
$$= 59\%$$

$$TOC\ Limit\ (Epinephrine) = 36.5\ ppm\ x\ 0.59$$
$$= 21.5\ ppm$$

The example illustrates that when starting with defensible clinical reference values, the MAC value for Epinephrine in Diazepam is 1.46 mg/dm^2. When TOC technology is deployed for a cleaning validation process, based on MAC and sampling method, the TOC limit for Epinephrine in Diazepam is determined to be 21.5 ppm.

conclusion

Based on recent guidance from the FDA, the life cycle approach should be considered best practice when implementing a cleaning validation process. The life cycle approach calls for continuous monitoring and updating to the design, qualification, and verification of the cleaning validation process. When choosing an analytical method to measure the effectiveness of the cleaning validation process, it should be noted that specific methods, looking at a single API, do not comply with the best practice recommendation as changes in other non-quantified contaminants will go unnoticed.

Nonspecific methods, such as TOC, comply with the best practice recommendation by measuring the total contaminants in the cleaning process rather than just a specific API. Degradants, excipients, and cleaning residues are just a few potential contaminants that are not captured in a specific method, such as HPLC, but are captured in a nonspecific method, such as TOC.

This chapter demonstrates that the determination of acceptance criteria limits for TOC in cleaning validation can be easily calculated and defended when starting from justifiable clinical reference values. This, in conjunction with the US FDA best practices for cleaning validation, highlights a few of the many appealing aspects driving industry leaders to adopt TOC analysis for cleaning validation on a large scale.

References

1. Guidance for Industry, Process Validation: General Principles and Practices. FDA, 2011, https://www.fda.gov/media/71021/download

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3. Guidance on Aspects of Cleaning Validation in Pharmaceutical Ingredient Plants. APIC Publications, APIC.cefic.org, https://apic.cefic.org/pub/APICCleaningValidationGuide-updateSeptember2016-final.pdf

TOC for Compendial Water Testing and Cleaning Validation; Comparison of Laboratory, At-Line, and Online Analysis

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Total organic carbon (TOC) and conductivity testing are important quality control measures for ensuring water purity and equipment cleanliness and can be deployed to accommodate various sampling scenarios and efficiency needs. TOC and conductivity analysis help manufacturers achieve compliance to USP <643> and USP <645>, or with process control needs. While conductivity is traditionally measured with a meter and probe, advanced TOC technologies can also offer conductivity measurements simultaneously with TOC analysis. The three common deployments of TOC technology are laboratory, at-line, and online analysis. When choosing which strategy and deployment are best for a unique application, consider the following to ensure you get the most out of the technology.

Laboratory analysis: TOC and conductivity analysis are routine tests that can be found in most Quality Control (QC) laboratories supporting cGMP operations. Benchtop TOC analyzers and software are available that allow users to stack protocols, run system protocols, run large volumes of samples at a time, manage data, and electronically sign and export data. Whether the TOC analyzer is being used for cleaning samples or water monitoring, efficiency is an important factor for most laboratories. For example, companies can now implement a "lean lab" solution that allows for simultaneous TOC and conductivity analysis from a single vial. Specialty vials are used to prevent ionic leaching from the vial surface and to prevent atmospheric CO_2 from dissolving into the sample. Both of these factors can cause over-reporting of conductivity. Traditional measurement of conductivity using a meter and probe can also introduce atmospheric CO_2 from having an open sample container while the measurement stabilizes. Meter and probe analysis is a very time-consuming methodology that requires analysts to test one sample at a time, wait for a stable reading, and then manually transcribe the data. Simultaneous TOC and conductivity testing ensures a lean lab and provides confidence in the data and data integrity while avoiding contamination risks. Whichever laboratory method is deployed, it is critical to have a properly calibrated and validated instrument if supporting cGMP operations. With laboratory analysis, it is inevitable that grab samples must be taken from equipment or purified water points of use. Additionally, QC laboratory workflow can take time - which is not conducive to efficient cGMP equipment turnover. With high frequency and high sample throughput, at-line or online analysis may satisfy the demand for efficiency gains in a monitoring program.

At-line analysis: At-line analysis can greatly increase process efficiency, particularly in a cleaning validation program with time constraints. At-line deployment uses a portable TOC analyzer located directly next to the process to be monitored. Once the cleaning process is complete, required samples are taken and can be analyzed almost instantaneously. This deployment is most successful for cleaning validation samples, particularly swabs, for monitoring time-critical operations. The laboratory workflow can be slow and clunky, creating unwanted equipment downtime. Coordinating activities with QC, sampling, analysis and release of data can leave equipment sitting idle for periods of time. To turn around equipment faster following cleaning, at-line analysis allows samples to be taken and immediately analyzed on a portable TOC analyzer located within reach. From there, swab and rinse sample results can be generated and reviewed within minutes, avoiding any delays from the QC workflow and reducing equipment hold times. At-line monitoring can provide efficiency gains for the right application in comparison to laboratory analysis. At-line avoids QC workflow and generates data within minutes following sample collection. For even greater efficiency, online analysis can enable real-time release of cGMP equipment and elimination of sampling activities all together. While at-line is a good fit for many applications, it limits the number of samples to be analyzed at a given time, which online analysis can overcome. Additionally, taking grab samples represents a single timepoint. To get multiple timepoints and a greater understanding of a process, online analysis may be the best deployment, generating multiple data points over time.

Online analysis: A pain point of cleaning validation is equipment downtime due to the work involved in sampling and sample analysis, as mentioned above. While time constraints can be improved upon with at-line deployment, online deployment facilitates instantaneous data generation and equipment turnover. Equipment downtime can be reduced from days to minutes with real-time release using data from a TOC analyzer integrated directly onto a Clean-In-Place (CIP) skid. Programmed automation diverts CIP rinse samples from the skid directly to the analyzer for analysis. The samples are analyzed, and data are automatically exported to the site data host. Online analysis is gaining momentum for cleaning validation for efficiency and quality gains, but it has been steadfast for compendial water testing. Online TOC and conductivity testing for purified water allows for reduction or elimination of point-of-use water sampling. Online analysis makes out-of-trend results highly detectable in real time, thus allowing for preventative and corrective actions. Whether for cleaning validation or compendial water testing, it is important to consider like-for-like technology to traditional laboratory analysis when moving to online analysis. Using the same technology online as is used in established laboratory methods simplifies the method transfer process. Rather than executing a full-blown method validation, an equivalency protocol can be performed to demonstrate suitable methodology from laboratory to online using the same validated technology.

Whether deploying laboratory, at-line, or online TOC analysis, consider your goals around efficiency, analytical performance, and data integrity. Equipment that can provide high accuracy, precision, and data integrity while offering opportunities to save you time will be the most valuable to your monitoring programs. While conductivity testing is often performed in the lab with a meter and probe, advances in analytical testing now enable conductivity to be measured simultaneously with other parameters to offer greater automation. TOC and conductivity are important quality metrics to understand and control the chemical purity of purified water and cleanliness of equipment. Advances in technology now allow TOC and conductivity monitoring to be faster and more reliable than ever.

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recovery of complex compounds with TOC: cleaning agents

introduction

The goal of any cleaning validation program is to reduce the opportunity for product contamination or compound carryover that may be present on production equipment. The validation of this type of process must prove that the cleaning process consistently removes product residue, process soils, potential contaminants, and excipients. It must also remove any degradants from cleaning agents and the cleaning agents themselves.

Two of the most common aqueous cleaning agents, alkaline or acidic, are considered one of the four primary cleaning parameters of a cleaning process. The critical parameters of cleaning are often referred to as time, action, concentration, and temperature (TACT)– where the cleaning agent's primary function is to create a "degradation" environment of all the process or product soils. Because of the degradation of these materials, a common industry practice is to use total organic carbon (TOC) as the analytical method to indicate removal of these compounds and the cleaning agents. Cleaning agents typically contain a very small amount of carbon (anywhere between 5-10%).

This application note investigates the appropriate steps to recover a complex compound like an alkaline cleaning agent and can be used as a template for feasibility testing or method validation elements as discussed in ICH Q2(R1).

TOC analysis for cleaning validation

Alkaline cleaning agents have been used to clean production equipment in the pharmaceutical, biopharmaceutical, cosmetic, medical device, dietary supplement, dairy, and food and beverage industries for decades. TOC analysis is a reliable measurement tool to measure and control how well the cleaning parameters (TACT) are performing. More specifically, TOC analysis may be used to measure the amount of organic residue left behind on the equipment surfaces being cleaned.

Analytical technologies used to measure TOC share the objective of completely oxidizing the organic molecules in a sample to carbon dioxide (CO_2), measuring the resultant CO_2 concentration and expressing this response as carbon concentration. A variety of laboratory and online technologies are available to measure TOC.

Sievers* TOC technology

The unique Sievers Membrane Conductometric detection method has proven to be an extremely reliable technique for measuring TOC. The Sievers technology uses a gas-permeable membrane that selectively passes only the CO_2 produced from the oxidation of organics. By preventing compounds such as acids, bases, and halogenated compounds from interfering with the measurement of CO_2 from oxidation, the Membrane Conductometric method delivers unmatched sensitivity, selectivity, stability, accuracy, and precision.

preparation of cleaning agent test standards

To test the recovery of alkaline cleaning agents with Sievers TOC Analyzers, stock solutions were created at various concentrations from 300 ppb C to 5 ppm C. This was done following recommendations of ICH Q2(R1) which emphasizes analyzing at least five concentrations for a linearity test and determining accuracy and precision during method validation.

100 ppm C stock solution: Precisely 1.08 mL of the alkaline cleaning agent was weighed into a cleaned, rinsed, and dried 500-mL glass volumetric flask. The cleaning agent was diluted to volume in the flask with low-TOC water (<50 ppb C). Preliminary analysis of three 0.01% dilutions of the alkaline cleaning agent used for this analysis showed the cleaning agent to contain approximately 4.6% carbon by mass. The conversion factors provided an accurate stock solution of 100 ppm C. This stock solution was used for 5 ppm C, 3 ppm C,1 ppm C, 0.5 ppm C, and 0.3 ppm C spikes.

Table 1 was used to accurately dilute the stock solutions in 100 mL volumetric flasks. Four sets of vials were created (20 vials) for this study. One set was used for the linearity test, and the remaining were used to determine percent recovery, accuracy, and intra-assay precision as described in ICH Q2(R1).

*Trademark of SUEZ; may be registered in one or more countries.

why Sievers™?

Gain complete TOC solutions and support for pharmaceutical applications with Sievers.

better TOC solutions

Sievers TOC Technology: Sievers Analyzers offer accurate measurements for compendial water testing, cleaning validation, and other pharmaceutical applications. We stand behind our time-tested technology to provide trusted TOC performance.

Data Integrity & Compliance: Our analyzers and software comply with 21 CFR Part 11 and meet, or exceed, recent data integrity guidelines.

Certified Vials and Standards: Sievers vials and reference materials minimize risks and eliminate variables in your analysis. From certified low TOC vials to pre-acidified and other specialty vials, we ensure top performance and accuracy.

unmatched support

Application Expertise: Sievers has dedicated experts to help you develop methods, determine feasibility, and implement new applications.

Installation & Validation Support: Get up and running more easily with our installation and validation services. Validation Support Packages for Qualification, Real-time Testing, and Cleaning Validation help you minimize startup delays.

On-Site Services: Maintain instrument performance and increase uptime with our customized service plans and visits from our Certified Field Service Engineers.

certified quality

Certified Reference Materials: ISO/IEC 17025 and ISO 17034 accreditations ensure our standards are consistently produced, controlled, and audited. Our Certificates of Analysis comply with strict guidelines and include all contributing factors to uncertainty.

Certified Plus: For the ultimate partnership, our Certified Plus plan offers comprehensive services, consumables, parts, and a fixed total cost of ownership.

Traceability: Sievers instrument health and failure analysis reports help you "close the loop" on TOC out-of-specifications. The complete traceability and corresponding documentation we offer is unmatched in the industry.

Whether you are monitoring TOC for regulatory compliance, real-time release, or cleaning validation, Sievers has a complete solution. We think outside the box to bring you to success.

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Table 1. Accurate Volume of Stock Solutions for Vials

Vial	Stock Used	Stock Volume (mL)	Total Weight Volume (mL)	TOC (ppm C)
1	100 ppm C	5	100	5.0
2	100 ppm C	3	100	3.0
3	100 ppm C	1	100	1.0
4	100 ppm C	0.5	100	0.5
5	100 ppm C	0.3	100	0.3

TOC analysis of cleaning agent test standards

The prepared cleaning agent test standards were then analyzed for TOC content. Each vial was analyzed with five replicates, with the first replicate being rejected. The average, standard deviation and percent relative standard deviation (% RSD) were calculated. The average of the water blank that was used to prepare the stock solutions was also recorded and factored into the final results. The blank value was used to subtract the water background from the test standard solution results.

Linearity Test Results

TOC Blank = 18 ppb C

Theoretical ppm C	Vial Set #1	% Recovery	% RSD
5.0	4.5	90%	0.56
3.0	2.7	89%	0.98
1.0	0.91	91%	0.97
0.5	0.46	91%	0.94
0.3	0.27	90%	0.83
Linearity Results	R^2= 0.999	Slope= 0.895	y-intercept = 0.003

Percent Recovery Results

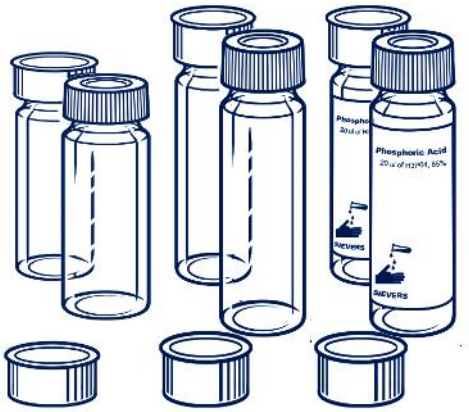
TOC Blank = 17 ppb C

Theoretical ppm C	Vial Set #2	Vial Set #3	Vial Set #4	% Recovery Average
5.0	101%	105%	94%	97%
3.0	105%	85%	92%	87%
1.0	102%	115%	101%	101%
0.5	104%	96%	99%	96%
0.3	101%	102%	107%	97%

summary

The data generated from this study demonstrate that alkaline cleaning agents can be analyzed for organic carbon content by TOC analysis with Sievers Analyzers. The analysis determined that the method is sensitive and linear over the 0.3 to 5 ppm C range, as demonstrated by an R^2 value of 0.999. Precision and accuracy were demonstrated with % RSD values less than three percent and average recovery values of 87% to 101%. The limit of detection was based on repetitive measurements of the reagent water used to make the stock solutions. This limit of detection for the analyte was determined to be 9.4 ppb C.

TOC analysis offers an effective way to measure cleaning agent and product residues, monitor cleaning processes, and reduce overall risks. Through its Sievers product line, SUEZ offers complete TOC solutions, services, and support for all your cleaning validation and verification needs.



what's your vial style?

get accurate TOC results with vials for all your applications

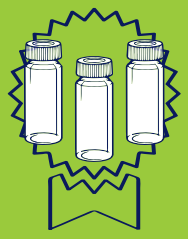
Whether you're testing for compliance, cleaning validation, or difficult-to-recover compounds, Sievers* TOC vials ensure top performance and minimize risks. **Accurate, efficient, & confident – that should be your style.**

- Certified, traceable, and guaranteed
- Manufactured by the global leader in TOC
- Backed by our OOS investigation support

Sievers Certified (<10 ppb TOC) Vials

for reliable, guaranteed quality

- The right choice for regulatory compliance testing
- Obtain accurate TOC results the first time and every time
- Pre-cleaned and certified (<10 ppb TOC)
- Backed by our OOS investigation support



Dual Use Conductivity & TOC (DUCT) Vials

for simultaneous compendial testing

- Suitable for simultaneous Stage 1 conductivity and TOC compliance testing
- Using a single vial and automation saves time, eliminates sample handling issues, and enhances data integrity
- Specialty coated glass and specialty septa, no ionic leaching, certified (<10 ppb TOC)
- Backed by our OOS investigation support

Pre-Acidified Vials

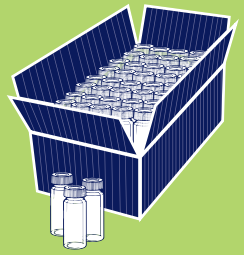
for sticky proteins and peptides

- Improve protein recoveries for cleaning validation applications
- Prevent adherence of proteins and peptides to vial surfaces
- Available in options for swab samples (pre-filled with acidified water) or for final rinse samples
- Backed by our OOS investigation support

Certified Blue Vials

for cleanrooms

- Used in controlled environments
- Paper free packaging, produced in an ISO 7 Cleanroom
- Certified Blue packaging available for Sievers Certified, DUCT, and Pre-Acidified Vials
- Backed by our OOS investigation support



SUEZ

selecting the best TOC sample vial for your application

Through its Sievers product line, SUEZ provides complete solutions for TOC analysis, including low-level TOC standards and a range of sample vials suitable for various applications. All scrupulously cleaned for low-level, the vials range from regular TOC certified vials to specialty coated or pre-acidified vials that can give superior TOC recovery on challenging protein applications.

TOC vial applications
USP, EP, JP, KP, and IP Purified Water and Water for Injection Testing
Cleaning validation, including swab recoveries
Method validation and development
Calibration and verification standards
Basic storage

Other vial companies offer only basic low TOC vials for TOC sampling use. SUEZ understands the importance of traceable, certified low TOC vials, but also realizes that these vials may not be best for all your specific application needs. For example, proteins and peptides are known to adhere to many glass and plastic surfaces, including typical borosilicate TOC sample vial containers that SUEZ and other companies provide as standard low TOC vials. This adherence can cause initial sample concentrations to be slightly lower and impact the accuracy and relative standard deviation of TOC measurements.

Sievers specialty TOC vials

Sievers developed two specialty vial types that fit the application needs of many customers: Pre-Acidified TOC vials and DUCT (Dual Use Conductivity & TOC) vials. Both vial types are certified and lot traceable, just like Sievers' heritage Certified TOC vials, but have been found to perform better on specific product families.

Sievers Pre-Acidified vials

- Case of 72 vials
- Automated, calibrated process for dispensing 20 µL of reagent grade phosphoric acid in each vial
- Acidifies sample to approximately pH 2.5, which impedes sample sticking to vial
- Each lot certified to <35 ppb TOC; 6-month shelf life
- Each 40 mL vial includes cap/septum with dust cap
- No Hazmat shipment; available in cardboard packaging or Certified Blue (cardboard free packaging)

Sievers DUCT vials

- Case of 30 vials
- Specialty coated glass vials developed for sensitive pharmaceutical formulations
- Specifically developed to avoid leaching and protein adsorption from samples
- Each lot certified to <10 ppb TOC and no ionic leaching
- Each 30 mL vial includes a specialty cap/septum with dust cap
- Available in cardboard packaging or Certified Blue (cardboard free packaging)

TOC vial comparison for mAb applications

A global biopharmaceutical company producing a specific monoclonal antibody (mAb) reached out to the SUEZ applications services laboratory to evaluate the most compatible vial for its cleaning validation studies. Samples of the mAb were sent to the

Recovery of a customer mAb in various vial types			
	Certified TOC vial	Pre-Acidified TOC vial	DUCT vial
100 ppb	74%	119%	59%
500 ppb	63%	95%	54%
1000 ppb	68%	93%	65%
1500 ppb	78%	97%	79%
3000 ppb	85%	93%	85%
5000 ppb	90%	95%	91%

Figure 1. Vial selection results for a global biopharmaceutical company

applications laboratory for testing and comparison in Sievers Certified TOC vials (<10 ppb), Pre-Acidified TOC vials (<35 ppb), and DUCT vials (<10 ppb and no ionic leaching). The results, as shown in Figure 1, demonstrate that the Sievers Pre-Acidified vials were best suited for this customer application.

vial suitability with common cleaning validation compounds

The SUEZ applications services laboratory tested many common compounds used in pharmaceutical and biopharmaceutical cleaning validation applications to compare recoveries in different vial types. The results from this testing are shown in Figure 2. Note that the suitability of the DUCT and Pre-Acidified vials varied across compounds. In some cases, the recoveries were equivalent and with other compounds the recovery was better in one vial type.

In response to these results, SUEZ developed the Vial Selection Guide[1] to help customers set up similar studies to determine the best vial for their applications.

The SUEZ applications services laboratory is also available as a resource for customers with vial selection needs. The applications laboratory can compare Sievers Pre-Acidified TOC vials, DUCT vials, and conventional Certified TOC vials using customers' specific compounds.

	Pre-Acidified TOC vial	DUCT vial
mAb	✓	
DNA		✓
Insulin	✓	
Terrific Broth	✓	✓
Urease	✓	✓
Hemoglobin	✓	

Figure 2. Suitability of Sievers specialty TOC vials for recovery of common cleaning validation compounds.

summary

Sievers Certified TOC, Pre-Acidified, and DUCT vials are:

- Cleaned using validated and automated equipment in an ISO 7 Cleanroom environment; vials are scrupulously cleaned of organic residues using low TOC reagent water
- Tested for minimal TOC background, and certified to <10 ppb (<35 ppb for Pre-Acidified vials) for use in critical applications including USP, EP water testing, and cleaning validation
- Available in the Sievers Certified Blue option, which eliminates paper and cardboard products as potential sources of microbial contamination in manufacturing and lab spaces

SUEZ provides complete solutions for TOC analysis, including both Pre-Acidified vials and DUCT vials in addition to traditional low TOC vials. Whether you're testing for compliance, cleaning validation, or difficult-to recover compounds, Sievers TOC vials ensure top performance and minimize risks.

References

1. Vial Selection Guide. SUEZ Water Technologies & Solutions, 2018, https://my.suezwatertechnologies.com/WTSCustomerPortal/s/content-download?DN=TBai_300_00332_EN.pdf

online cleaning validation for real-time equipment release using total organic carbon, inorganic carbon, and conductivity data

overview

Cleaning validation is an important element to cGMP manufacturing to ensure purity, quality, and potency of drug product. Above all, patient safety is the primary concern. Demonstrating a validated cleaning process has been a regulatory requirement for many years. Today, many manufacturing facilities still follow the historical practice of capturing grab samples and swabs for laboratory analysis for total organic carbon (TOC) and conductivity to satisfy this requirement.

While compliant, this traditional method of cleaning validation is time consuming, leaves room for error, and reduces capital equipment utilization. Thus, the industry is embracing online cleaning validation as a more efficient and sustainable monitoring program for cleaning validation and verification. The following outlines SUEZ's solution for a lean, well-defined, defensible cleaning validation and verification program using the Sievers M9 Analyzer for TOC and conductivity.

today's challenges

Traditionally, cleaning validation and verification have been accomplished by manual sampling and laboratory analysis. This workflow poses significant quality and efficiency shortfalls:

- Grab samples are time consuming and require analyst resources to prepare sample containers, print sample labels, collect samples, transport samples to the lab to begin analysis, and complete data entry and review. Swab technique also requires extensive validation and training for proper recovery.
- Sample integrity can be compromised by sampling and laboratory workflow. Contamination risks and sample storage stability need to be assessed in any program taking grab samples.
- Laboratory workflow frequently results in delayed data release, prolonging equipment downtime.
- Grab samples have the limitation of representing a single timepoint rather than providing a comprehensive understanding of cleaning cycles.

Process Analytical Technology

In 2004 the FDA published a guidance document on Process Analytical Technology (PAT).[1] This document contains non-binding recommendations and serves to encourage cGMP manufacturers to deploy PAT to achieve process understanding, process control, and continuous demonstration of a validated state. PAT allows for real-time measurements of desired quality attributes. Using real-time data enables process understanding and demonstration of a validated state without manual sampling or laboratory analysis.

Rather than testing to a predetermined timepoint, PAT allows for the evaluation of cleanliness based on an acceptable measurement of quality attributes. Deploying PAT enables companies to optimize their cleaning validation programs to reduce cleaning time, cleaning agents, water usage, equipment downtime, and human error involved in a cleaning program. PAT is subject to the same level of scrutiny from the FDA, so it is critical to have a fully validated and compliant system to assess cleanliness and release equipment.

analyzer versus sensor

When choosing appropriate online technology, it is important to understand the application and regulatory guidance. To use PAT to the full capability of real-time equipment release, it is essential to have a validated instrument that satisfies instrument qualification, method validation, and Data Integrity requirements.

The vast majority of online TOC instruments employ conductivity as a means to measure carbon. Sievers TOC Analyzers, such as the Sievers M9, are carbon analyzers, wherein a gas-permeable membrane separates interfering compounds from CO_2 to allow for accurate measurement of carbon. This technology instills confidence in the accuracy and precision of the measurement.

Sensors work by measuring conductivity pre-oxidation and post-oxidation. While many TOC instruments measure conductivity pre- and post-oxidation in some manner, sensors measure the resultant conductivity without any level of discrimination against interfering ions. The difference in conductivity is attributed to TOC, even though other species (not carbon) may be contributing to the measurement. This leads to over- or under-reporting when interfering substances, often present in cleaning processes, are in the sample (Figure 1).

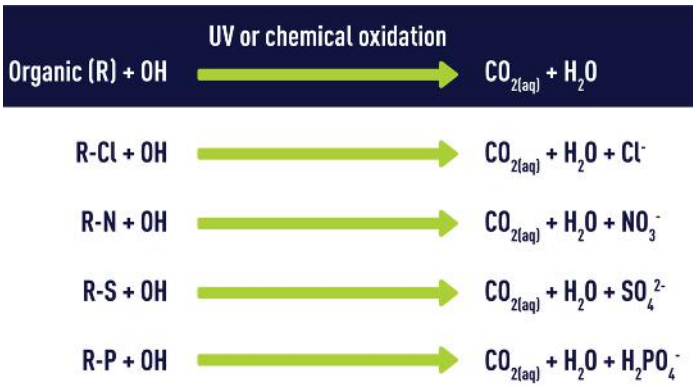


Figure 1. APIs, degradants, cleaning agents, or excipients could also be present in a rinse sample. Molecules bonded to organic carbon molecules are also subject to oxidation.

With sensor technology, not only is there a risk of false reporting, but sensors can present compliance and efficiency concerns when attempting calibration, qualification, or maintenance. For example, sensor methods cannot be validated per ICH Q2 (R1) when attempting to demonstrate linearity and specificity. Analytical method validation is a critical component needed to use data for cGMP release. Calibration, system suitability, and maintenance can be lengthy processes, requiring attachments or even shipment of an instrument to the manufacturer. Sievers M9 maintenance, calibration, and system suitability are entirely self-contained with field support for onsite validation, maintenance, and troubleshooting activities.

The Sievers M9 reports validated and accurate TOC data in addition to simultaneously quantifying inorganic carbon and conductivity. Having data on these three quality attributes offers a robust view into a cleaning process.

the SUEZ solution

Together, total organic carbon, inorganic carbon, and conductivity provide a comprehensive understanding of a cleaning process. These three attributes can be assessed collectively to optimize, troubleshoot, or investigate out-of-specification (OOS) results. Once control ranges of each attribute are established from validated data, departure from process control or specification can be quickly identified and corrected. Data can be used together to determine possible root cause as shown in Figure 2.

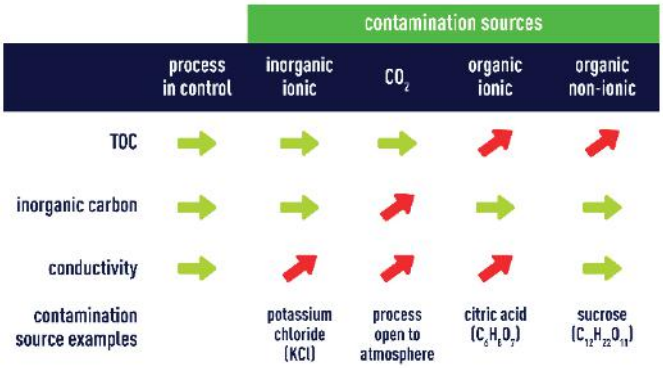


Figure 2. Collectively TOC, inorganic carbon, and conductivity improve detection of out-of-trend results as well as focusing root cause investigations.

To demonstrate M9 integration and communication with a Clean-In-Place (CIP) skid for real-time, online analysis and data reporting, a Sievers M9 Portable TOC Analyzer was integrated with a CIP skid in SUEZ's UltraFlow 45 CIP Skid in SUEZ's Analytical Instruments development laboratory in Boulder, Colorado (Figure 3).

Flow, pressure, timing, and cleaning methods were adjusted to mimic common cleaning processes used by manufacturers. The resulting solutions address complex sampling logistics that companies face. Whether they are time, volume, or pressure constraints, the Sievers M9 can be successfully integrated and automated with SUEZ kits for either pressurized sampling or non-pressurized sampling. It is also important to note that the M9 Portable Analyzer is the same technology as the M9 Laboratory Analyzer. When moving from lab analysis to online, like-for-like M9 technology streamlines the method transfer process and eliminates the need for a full method validation.

mitigating contamination

Following sample analysis, it is important to consider the risk of microbial contamination in the sample flow path and take measures

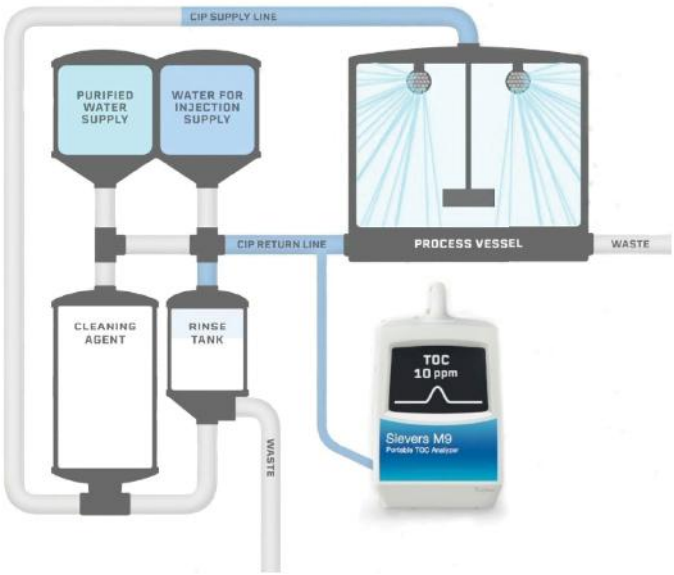


Figure 3. Sievers M9 Portable TOC Analyzer integrated with a CIP skid for real-time rinse analysis.

to mitigate that risk. Sievers M9 integration mitigates the risk of microbial contamination in the sample flow path without additional parts or processes.

Pneumatic valves and clean compressed air are used to completely dry the sample flow path between cleaning cycles. The sampling kit and the M9's Integrated Online Sampling (iOS) system can also tolerate steam sterilization, hot water, and harsh cleaning agents regularly used in cGMP processes. With the Sievers M9 online cleaning validation configuration, clean compressed air is blown through the sample flow path to leave it clean, dry, and ready for the next analysis. This offers an automated solution to manage and mitigate contamination risk within the online cleaning validation integration.

validation and Data Integrity

Online cleaning validation with the Sievers M9-CIP integration provides a compliant and lean approach to regulatory requirements. Sievers Validation Support Packages I and II satisfy all requirements for instrument qualification to ensure the generated data are accurate and can be used to release critical cGMP equipment.

Data Integrity continues to be a central and growing topic in cGMP facilities. Sievers M9 TOC Analyzers with DataGuard satisfy compliance to 21 CFR Part 11 and Data Integrity guidelines. Various user levels with modifiable permissions ensure correct access levels for all users. The audit trail captures all activities performed on the instrument, when activities were performed, and by which unique user. Data, methods, and audit trails cannot be modified or deleted. DataGuard allows for real-time data to be analyzed, stored, or transferred in a Data Integrity compliant manner.

summary

With pressure to meet today's production demands, many companies are embracing Process Analytical Technology (PAT) for operational efficiencies and lean processes. Online cleaning validation offers process understanding, process control, risk management, efficiency gains, and optimization that cannot be achieved with laboratory monitoring.

To make the most of cleaning validation data, the Sievers M9 offers precise, accurate, quantitative, and robust analysis. With validated and accurate results, data can be used to make important decisions, release equipment real-time, troubleshoot, and optimize the cleaning process in a compliant manner which addresses Data Integrity concerns.

SUEZ, through its Sievers product line, offers a turnkey solution to online cleaning validation inclusive of instrumentation, validation, compliance, technical support, OOS support, standards, kits for installation, and applications support.

For more information or to contact SUEZ for a feasibility assessment of your process, visit https://www.suezwatertechnologies.com/lp-ai-olcv

References

1. Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. FDA, 2004, https://www.fda.gov/media/71012/download

conclusion

Total organic carbon and conductivity are important quality metrics for assessing cleanliness of equipment. Whether new to cleaning validation, moving from HPLC to TOC or laboratory analysis to online, SUEZ has a multitude of resources to ensure your success. These resources include onsite applications support, validation packages, failure analysis reporting, tech support, and assistance with recovery or soiling studies through SUEZ's applications lab. For more information or to get in touch visit

www.suezwatertechnologies.com/sievers