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Simplifying Cleaning Validation: How TOC Streamlines Residue Detection

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Outline

- What is Cleaning Validation
- Why is it Important
- Regulatory Requirements
- Brief History
- Cleaning Validation Process Overview
- Fundamentals of TOC Analysis
- TOC and Cleaning Validation
  - Advantages and Limitations
  - Recovery and Background Correction
  - Example Calculations

What is cleaning validation?

- Cleaning validation is the process of providing **documented evidence** that cleaning procedures **consistently** and effectively remove product residues, contaminants, microorganisms, and cleaning agents from equipment, surfaces, or manufacturing systems to a **predetermined acceptable level**.

Why is cleaning validation Important?

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- At its core, cleaning validation is the process of confirming that equipment, utilities, and facilities that may come into contact with the drug manufacturing process are effectively cleaned to control cross-contamination and ensure:
  - patient safety
  - product efficacy
  - quality
- The goal is to establish practical and reliable methods that comply with current good manufacturing practices (cGMPs).

Why is cleaning validation Important?

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- The purpose is to ensure that:
  - Product carryover from a previous batch does not contaminate the next batch.
  - Cleaning agents (detergents, solvents, disinfectants) are removed adequately.
  - Microbial contamination is controlled.
  - Equipment is safe and suitable for its intended use.
  - Regulatory requirements (FDA, EMA, GMP, etc.) are met.

Cleaning Validation – A Regulatory Requirement

- Not just best practice - It is a regulatory requirement
- As the FDA states:
  - "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (21 CFR 211.67[a], 2014).
- In the EU:
  - GMP Annex 15 includes specific guidance on qualification and validation and contains a dedicated section on cleaning validation, making it an established regulatory expectation
- Cleaning validation is widely applied in industries such as pharmaceuticals, biotechnology, food, and medical devices.
- When cleaning validation fails, the risks are real. Failure to control cross-contamination in pharma can lead to product recalls, reputational damage, and in severe cases, patient injury or death.

§ 211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51931, Sept. 8, 2008]

10. CLEANING VALIDATION

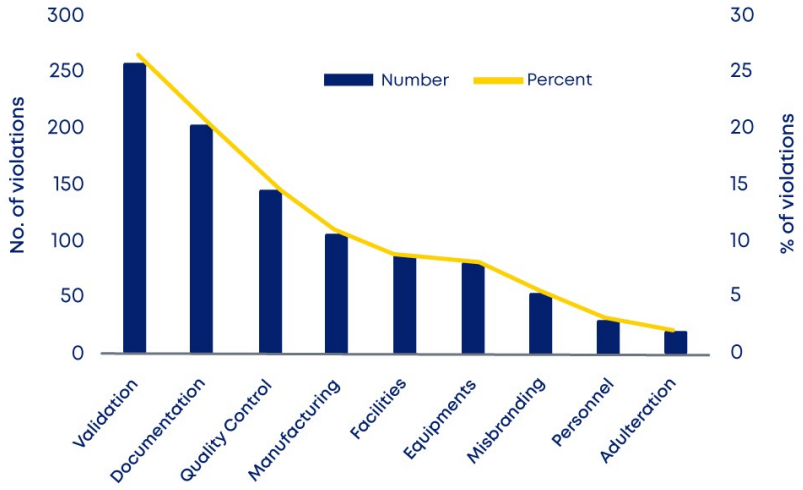
10.1. Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.

10.2. A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

10.3. It is recognised that a cleaning validation programme may take some time to

Cleaning Validation – A Regulatory Requirement

- Validation-related deficiencies continue to be among the most frequently cited FDA inspection observations.
- Between 2010 and 2020, approximately 25–30% of FDA warning letters referenced validation-related issues (Rathore et al., 2022).
- Cleaning validation remains a significant contributor to regulatory observations.
- Common FDA findings include:
  - Inadequate validation protocols
  - Unsupported acceptance limits
  - Poor sampling strategies
  - Incomplete documentation
  - Failure to investigate deviations
  - Insufficient ongoing monitoring



Why is cleaning validation Important?

In summary why is managing a robust cleaning validation program in a manufacturing facility so important?

- Key reasons to prioritize a robust cleaning validation system include:
  - Patient safety: Residual contamination can pose health risks, particularly for parenteral and inhalable medicines.
  - Product quality and efficacy: Preventing contamination maintains high product safety and efficacy standards.
  - Regulatory compliance: A well-documented, science-based process is fundamental to passing inspections under FDA cleaning validation guidelines. Noncompliance can lead to warning letters, import alerts, or other serious penalties.
  - Reputation and trust: Strong cleaning validation practices protect a company's standing with regulators, customers, and partners.
  - Operational efficiency: Effective programs minimize downtime, reduce batch rejections, and improve productivity and batch throughput.
  - Product integrity: Rigorous cleaning validation ensures products consistently meet their target quality profiles.

Cleaning Validation – Evolution of Cleaning Validation

- The concept of cleaning validation in pharma has evolved significantly over the decades, driven by increasing regulatory oversight and the need for stronger product safety measures.
- Initially, cleaning processes were largely unregulated, relying on general best practices rather than formalized validation methods.
- However, as pharmaceutical manufacturing expanded and product complexity grew, regulators introduced stringent requirements to prevent cross-contamination and ensure product integrity.
- Understanding this history helps manufacturers appreciate the rationale behind today's regulatory expectations and why cleaning validation continues to be a critical focus for manufacturing facilities.

History of Cleaning Validation – 1960s to Present

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1960s

GMP regulations require clean equipment.

- The Era of Visual Inspection

1978

cGMPs formalize equipment cleaning requirements.

- Cross-contamination incidents
- Establish procedures for cleaning and equipment maintenance

1987

FDA process validation guidance strengthens validation culture

- Increased regulatory focus on validation

1988

Cholestyramine contamination recall highlights cross-contamination risks.

- Further contamination incidents drive change
- Emergence of modern validation concepts

1990s

Standardization and Emergence of Cleaning Validation Guidelines

- The Barr Lab Decision
- 1993 FDA cleaning validation inspection guide published
- 10 ppm Acceptance Criteria
- Global Harmonization

2000s

Science and Risk Based Cleaning Validation

- Risk-based methodologies
- Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- Global Harmonization

2014/15

Shift toward toxicology-based cleaning limits

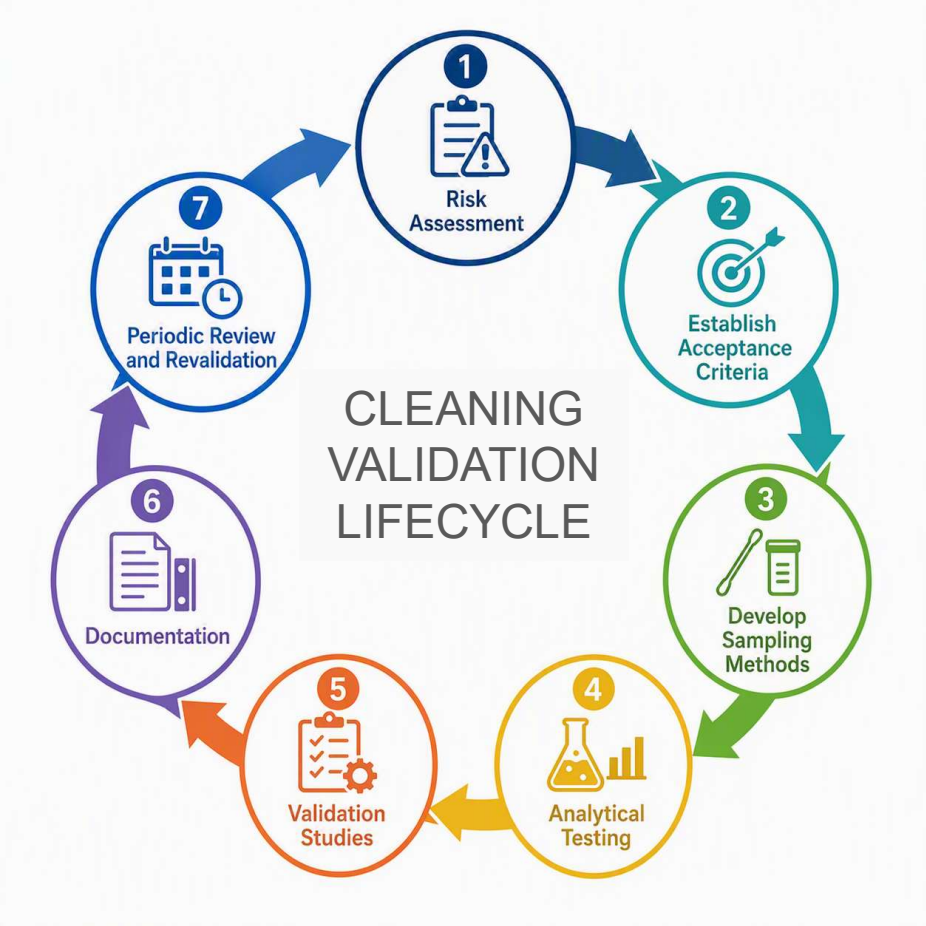
- Health-based Exposure Limits (HBELs)
- Revised EU Annex 15

Present

Lifecycle and Contamination Control Focus

- Continuous monitoring
- Periodic review and revalidation
- Data integrity
- Risk management
- Contamination Control Strategies (CCS)

Cleaning Validation Lifecycle



1. Risk Assessment
2. Establish Acceptance Criteria
3. Develop Sampling Methods
4. Analytical Testing
5. Validation Studies
6. Documentation
7. Periodic Review and Revalidation

Cleaning Validation Process

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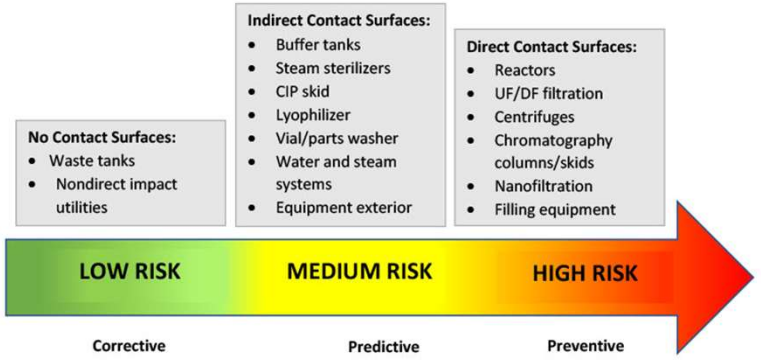
- **Risk Assessment**
  - Identify:
    - Worst-case products
      - Highest cleaning risk
        - Poor Solubility, High toxicity, Strong Adhesion, Strong Odors
    - Hardest-to-clean equipment
      - Complex design, crevices, inaccessible surfaces
      - Valves, Gaskets, Filters, Seals
      - Poor Drainage
    - Most potent compounds
      - Consider Toxicological Data, HBELs, OELs, Genotoxicity…etc
    - Shared manufacturing equipment
      - Presents the greatest risk for cross-contamination
      - Consider manufacturing sequence and changeovers



Cleaning Validation Process

- Establish Acceptance Criteria
  - Scientifically justified
  - Risk-based
  - Compliant with current regulatory expectations
  - Determine maximum allowable residue levels using approaches such as:
    - Health-Based Exposure Limits (HBELs)
    - PDE (Permitted Daily Exposure)
    - MACO (Maximum Allowable Carryover)
  - Additional Considerations
    - Cleaning agent residues
    - Degradation products and intermediates
    - Microbial contamination (where applicable)
    - Visual cleanliness requirements
    - Analytical method detection and quantitation limits
    - Equipment design and sampling recoveries

Note: The final acceptance criteria should represent the most stringent and scientifically defensible limit while remaining measurable using validated analytical methods

Cleaning Validation Process

Develop Sampling Methods

Swab Sampling

- Surface is physically swabbed and analyzed
- When to Use:
  - Higher sensitivity
  - Allows evaluation of specific and focused high-risk locations
  - Enables determination of residue levels per unit area (e.g., µg/cm²)
  - Identify localized cleaning failure
- Common Applications:
  - Areas with welds, joints, seals, and crevices
  - Regions with poor cleaning solution coverage
  - Locations identified through risk assessment

Rinse Sampling

- Final rinse water is collected and analyzed
- When to Use:
  - Inaccessible areas
  - Complex internal surfaces
  - Large systems and fluid pathways
  - Minimal equipment disassembly
  - Clean-in-Place (CIP) systems
- Common Applications:
  - Transfer lines and piping systems
  - Tanks with limited access
  - Mixers and reactors with complex geometries
  - Valves, pumps, and enclosed processing equipment

Combined Sampling Strategy

In many cleaning validation programs, both swab and rinse sampling are used to maximize confidence and robustness in cleaning effectiveness.

Cleaning Validation Process

- Analytical Testing
  - HPLC
    - Widely used due to its high sensitivity and specificity for product-related residues
  - TOC (Total Organic Carbon)
    - Measures the total amount of organic material present in a sample rather than targeting a specific compound
    - Excellent nonspecific screening tool for monitoring cleanliness
  - UV-Vis Spectroscopy
    - Measures the absorption of ultraviolet or visible light by a substance and can be used to quantify residues
    - Effective for compounds with strong UV or visible light absorbance
  - Conductivity
    - Measures the electrical conductivity and is particularly useful for detecting ionic residues, cleaning agents, and detergent remnants
  - Microbial testing
    - May be necessary to ensure that cleaning processes adequately control microbial contamination

Note: In many cleaning validation programs, multiple analytical techniques are used together to provide comprehensive assessment of equipment cleanliness.

Cleaning Validation Process

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- Validation Studies
  - The cleaning validation itself will usually consist of the previously mentioned risk assessment, acceptance criteria, and sampling and analytical method development and validation.
  - A common approach on execution is:
    - Typically, three consecutive successful cleaning cycles under routine operating conditions to demonstrate reproducibility.
    - Hold time studies
      - Dirty hold time: maximum time equipment may remain uncleaned after use.
      - Clean hold time: maximum time cleaned equipment may be stored before reuse.
    - Sampling of worst-case and hard-to-clean locations.
    - Collection and analysis of swab samples, rinse samples, or both
    - Final validation report demonstrating acceptance criteria were met.
    - Outline of ongoing and routine monitoring, periodic review to assess trends, deviations, changes, and continued suitability.
    - Define what will trigger revalidation.

Cleaning Validation Process

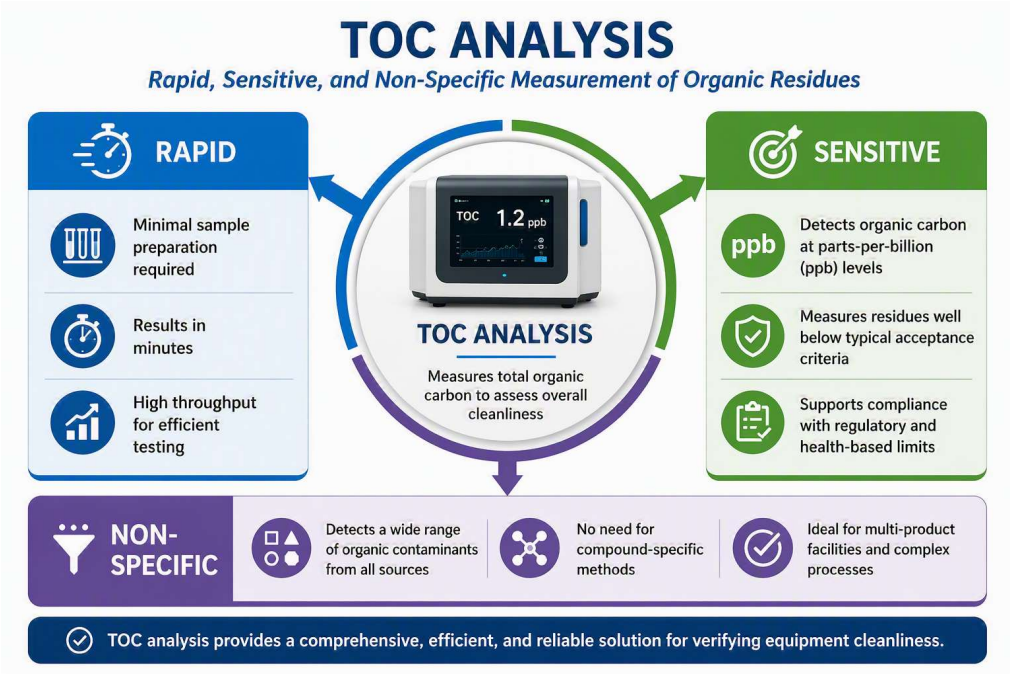
- Documentation
  - Risk Assessment
  - Validation Protocol
    - Acceptance Criteria
    - Sampling locations
  - Sampling Methods
  - Analytical Test Methods
  - Validation Summary Report
    - Results
    - Deviations
  - Periodic Reviews and Re-Validations

Cleaning Validation Process

- Periodic Review and Revalidation
  - Not typically repeated on a fixed regulatory schedule.
  - Revalidation is performed when there is evidence that the validated state may no longer be maintained.
  - FDA guidance expects validation programs to define when/what might trigger revalidation.
  - Common Triggers:
    - Changes to equipment design or configuration
    - Changes to the cleaning procedure, agents or concentrations
    - Introduction of new products
    - Repeated cleaning failures, deviations, or adverse trends
    - Extended equipment hold times beyond validated limits.
  - Periodic Review
    - Regardless of changes companies are expected to perform periodic reviews of cleaning validation to verify the process remains in control.
    - Many firms conduct these reviews annually.

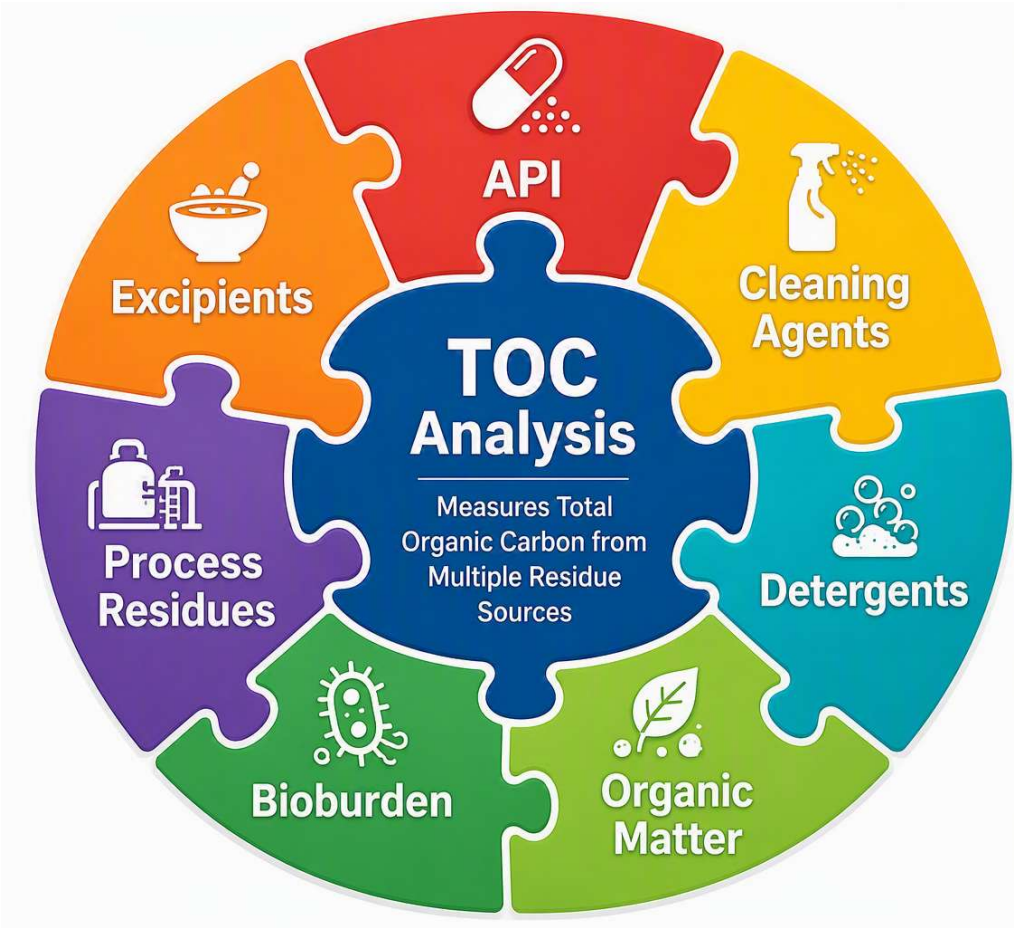
TOC and Cleaning Validation

- Total Organic Carbon (TOC) is an effective analytical method in **pharmaceutical cleaning validation** because it provides a **rapid, sensitive, and non-specific measurement of organic residues** that may remain on manufacturing equipment after cleaning.



TOC and Cleaning Validation

1. **Detects a Wide Range of Organic Contaminants**
   - TOC measures the total amount of carbon present in organic compounds, allowing it to detect:
     - Active pharmaceutical ingredients (APIs)
     - Excipients
     - Cleaning agents and detergents
     - Process residues
     - Bioburden-related organic matter
   - Because many pharmaceutical residues contain carbon, TOC can verify equipment cleanliness without requiring a separate test for every possible contaminant.



TOC and Cleaning Validation

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2. High Sensitivity

- Modern TOC analyzers can detect organic carbon at parts-per-billion (ppb) levels, making them capable of measuring residue levels well below typical cleaning acceptance criteria.
- This sensitivity helps ensure compliance with stringent regulatory expectations and health-based exposure limits

3. Rapid Analysis

- Compared with compound-specific methods such as HPLC:
  - Minimal sample preparation is often required.
  - Results are obtained quickly (typically minutes).
  - Sample throughput is high.
- This allows faster turnaround during cleaning validation studies and routine monitoring.

TOC and Cleaning Validation

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4. Non-Specific Screening Tool

- TOC does not need prior knowledge of the exact residue composition. This is particularly useful when:
  - Multiple products are manufactured on the same equipment.
  - Cleaning processes remove a variety of organic materials.
  - A general verification of cleanliness is needed.

5. Suitable for CIP and Rinse Sampling

- TOC is especially valuable for:
  - Final rinse water analysis
  - Clean-in-place (CIP) system monitoring
  - Verification of cleaning process consistency

- Since rinse samples can be analyzed directly, TOC provides an efficient means of assessing residue removal from complex equipment surfaces

TOC and Cleaning Validation

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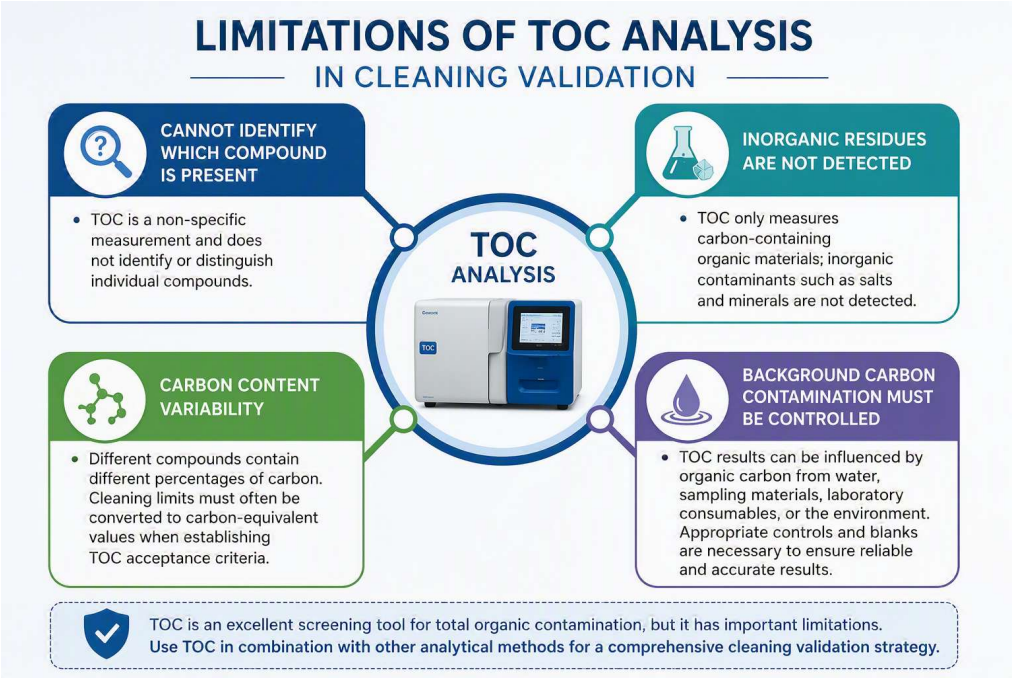
6. Regulatory Acceptance

- Regulatory agencies and industry guidance recognize TOC as a useful cleaning validation tool when scientifically justified.
- It is frequently used alongside:
  - Visual inspection
  - Specific analytical methods (HPLC, LC-MS)
  - Conductivity testing
  - Swab recovery studies

Limitations of TOC

- **Limitations**
  - TOC is not always sufficient as a stand-alone method because:
    - It cannot identify which compound is present.
    - Inorganic residues are not detected.
    - Different compounds contain different percentages of carbon, requiring carbon-content calculations when establishing limits.
    - Background carbon contamination from water or sampling materials must be controlled.



Advantages of TOC

- **Non-Specific vs Product-Specific Assays**

TOC ANALYSIS vs. PRODUCT-SPECIFIC METHODS (e.g., HPLC)

Two Complementary Approaches for Effective Cleaning Validation

TOC ANALYSIS (Non-Specific)	KEY ADVANTAGE	PRODUCT-SPECIFIC METHODS (e.g., HPLC)
RAPID RESULTS Results in minutes with minimal sample preparation.	SPEED	Longer run times and more extensive sample preparation.
NON-SPECIFIC DETECTION Measures total organic carbon; detects a wide range of organic residues.	SCOPE OF DETECTION	Measures specific target compounds only; may miss unknown or unexpected residues.
SIMPLE METHOD DEVELOPMENT One method applicable to many products and residue types.	METHOD DEVELOPMENT	Requires development and validation for each specific compound.
IDEAL FOR MULTI-PRODUCT FACILITIES Effective for equipment used for multiple products.	MULTI-PRODUCT APPLICABILITY	Not practical for routine monitoring of many products on shared equipment.
COST-EFFECTIVE Lower per-sample cost and reduced laboratory resources.	COST & RESOURCES	Higher cost due to consumables, standards, and extended labor time.
WELL SUITED FOR RINSE & CIP SAMPLES Excellent for final rinse water and CIP system monitoring.	CIP / RINSE APPLICATIONS	Less suitable for rinse samples due to lower sensitivity and matrix effects.
WIDELY ACCEPTED WHEN JUSTIFIED Recognized by regulators as a valuable cleanliness assessment tool.	REGULATORY ACCEPTANCE	Required when compound identity, quantitation, and low acceptance limits are needed.

KEY TAKEAWAY: TOC analysis offers a fast, broad, and cost-effective assessment of overall organic contamination, while product-specific methods like HPLC provide targeted identification and quantitation of individual compounds.
Using both approaches together creates a comprehensive and scientifically sound cleaning validation strategy.

TOC and Cleaning Validation - MACO

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How is TOC Limit Calculated for a Specific Residue?

- The first step is to determine the maximum amount of residue that can safely remain on equipment after cleaning.
- This limit is commonly based on a health-based approach using the Maximum Allowable Carryover (MACO) calculation.
- **Step 1: Determine the Residue Acceptance Limit**
  - Commonly, the acceptable residue is calculated using a health-based approach such as:

$$\text{MACO} = \frac{PDE \; x \; Minimum \; Batch \; Size \; of \; Next \; Product}{\text{Maximum Daily Dose } of \; Next \; Product}$$

where:

MACO = Maximum Allowable Carryover
PDE = Permitted Daily Exposure of the residue
Minimum Batch Size = Minimum batch size of next product
Maximum Daily Dose = Maximum daily dose of next product

TOC and Cleaning Validation – Carbon Fraction

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Step 2: Convert Residue Limit to Carbon Limit

Since TOC measures carbon rather than the compound itself, calculate the fraction of carbon in the residue molecule:

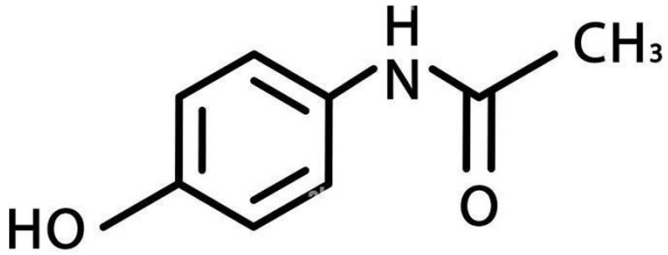
$$\text{Carbon Fraction} = \frac{\text{Molecular Weight of Carbon Atoms}}{\text{Molecular Weight of Compound}}$$

Example:

For acetaminophen (paracetamol):

- Molecular formula: $C_8H_9NO_2$
- Molecular weight = 151.16 g/mol
- Carbon contribution = 8 × 12.01 = 96.08 g/mol
- "Carbon Fraction“ = 96.08/151.16=0.636

So acetaminophen is approximately 63.6% carbon



Paracetamol
$C_8H_9NO_2$

TOC and Cleaning Validation – TOC Limit

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Step 3: Calculate the TOC Limit

- Suppose the following residue limit:

$$\text{MACO} = 12.5 \text{ mg acetaminophen}$$

Then:

$$\text{TOC Limit} = 12.5mg \times 0.636$$

$$= 7.95 \text{ mg C}$$

The TOC acceptance criterion for acetaminophen would therefore be:

$$\boxed{7.95\ mg\ C}$$

TOC and Cleaning Validation – Swab TOC Limit

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Step 4: Convert the TOC Limit

- **For Swab Samples**

Surface TOC Limit $= \frac{TOC\ Limit\ (MACO\ x\ carbon\ fraction)}{SURFACE\ AREA}$

$= \frac{7.95\ mg\ C}{25{,}000\ cm^2} = 0.000318 \frac{mg\ C}{cm^2}$

If the swab area is 25cm^2 and Swab Recovery is 80%:

$= \frac{Surface\ TOC\ Limit \frac{mg\ C}{cm2} \times Swab\ Area\ cm^2}{Swab\ Recovery\ (\%)}$

$= \frac{0.000318 \frac{mg\ C}{cm2} \times 25\ cm^2}{0.80} = 0.00636\ \text{mg C}$

More to come on swab recovery

Finally convert the residual TOC Limit into a TOC concentration:

$= \frac{TOC\ (mg\ C)}{Extraction\ Volume\ (mL)} \times 1000 \frac{mL}{L}$

$= \frac{0.00636\ (mg)}{40\ (mL)} \times 1000 \frac{mL}{L} =$ **0.159 mg/L or 159 ppb**

Don't Forget about Correcting for Background TOC Contribution

TOC and Cleaning Validation – Rinse TOC Limit

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Step 5: Convert the TOC Limit

- **For Rinse Samples**

Rinse TOC Limit (adjusted for Rinse Recovery):

$$= \frac{MACO \times Carbon\ Fraction \times Rinse\ Recovery\ (\%)}{Final\ Rinse\ Volume\ (L)}$$

$$= \frac{12.5\ mg \times 0.636 \times 0.90}{100\ L}$$

$$= \mathbf{0.072}\ \frac{\boldsymbol{mg\ C}}{\boldsymbol{L}}\ \boldsymbol{or\ 72ppb}$$

Don't Forget about Correcting for Background TOC Contribution

TOC and Cleaning Validation

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- **Additional Considerations**
  - When setting a validated TOC Limit, laboratories should also account for:
    - Background TOC in the rinse or extraction water
    - Residual TOC present in the extraction vial, coupon or on the swab
    - Swab and rinse sampling recovery factors
    - Swab extract dilution factors (if applicable)
    - Instrument detection and quantitation limits
    - Method validation requirements
  - Thus, the final operational TOC acceptance criteria may be adjusted from the theoretical carbon limit to reflect actual method performance.

TOC and Cleaning Validation – Swab Recovery

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- **Sampling Recovery Factors**
  - A recovery factor accounts for the fact that sampling methods rarely recover 100% of the residue present on an equipment surface. During swab sampling, some residue may remain on the surface, remain trapped in the swab material, or be lost during extraction and analysis.
  - The recovery factor is therefore used to correct analytical results and provide a more accurate estimate of the actual amount of residue present.

  - **Step 1:** Perform a Recovery Study
    - A known amount of residue is applied to a representative equipment surface (coupon) and allowed to dry under controlled conditions.
    - The surface is then sampled using the same:
      - Swab material
      - Sampling technique
      - Extraction procedure
      - Analytical method

TOC and Cleaning Validation – Swab Recovery

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- **Step 2: Calculate Percent Recovery**
  - The recovery percentage is calculated by comparing the amount recovered to the amount originally applied.

$$\text{Percent Recovery} = \frac{\text{Amount Recovered}}{\text{Amount Applied}} \times 100$$

Example

Known spike applied to coupon: $= 100\ \mu g$

Measured after swabbing and extraction: $= 80\ \mu g$

Recovery: $= \frac{80 \mu g}{100 \mu g} \times 100 = 80\%$

  - Conversely: a correction factor can be calculated which is just the inverse of the Percent Recovery:

$$\text{Correction Factor} = \frac{Amount\ Applied}{Amount\ Recovered}$$

$$\text{Correction Factor} = \frac{100}{80} = 1.25$$

TOC and Cleaning Validation – Swab Recovery

- **Step 3: Correct Sample Results**
  - During routine testing, the measured result can be adjusted to estimate the actual residue level.

$$\text{Corrected TOC Residue} = \frac{\text{Measured TOC Residue}}{\text{Recovery Fraction}}$$

or

$$\text{Corrected TOC Residue} = \text{Measured TOC Residue} \times \text{Correction Factor}$$

Example

Measured TOC Residue:

$$4\,\mu g/cm^2$$

Recovery:

$$80\%$$

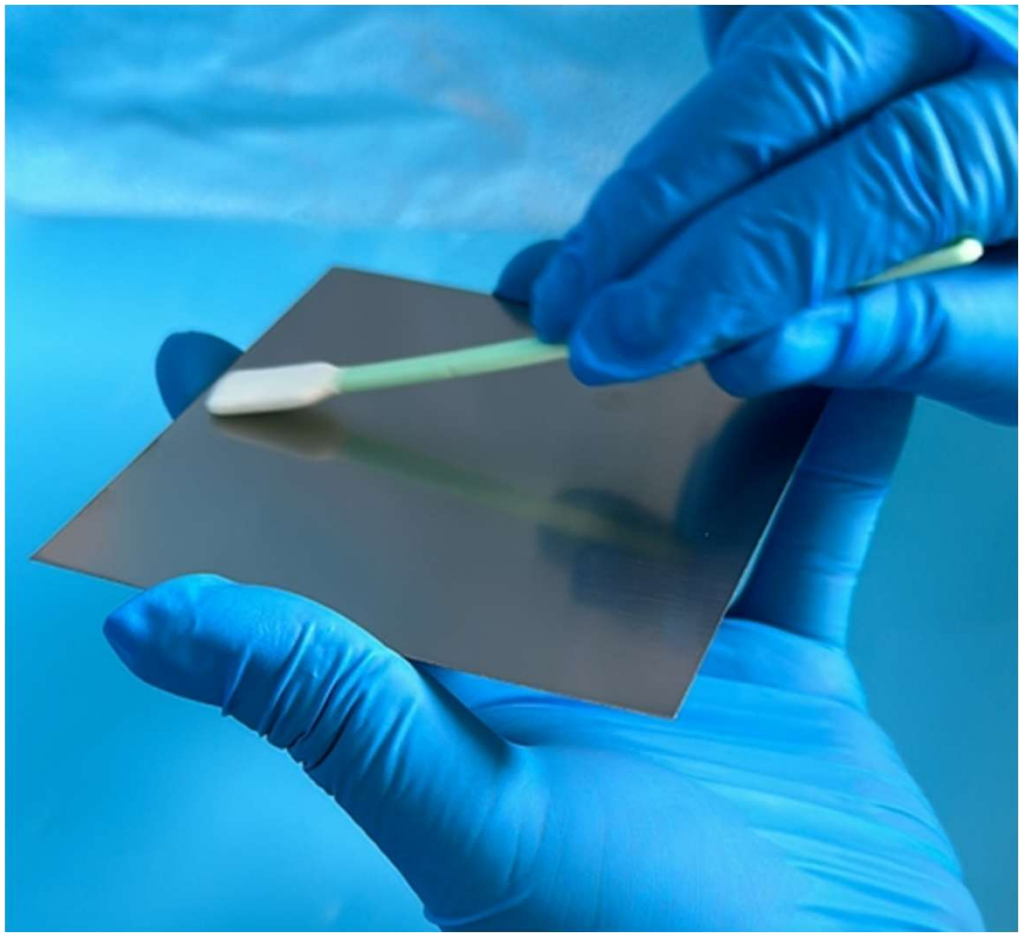
Corrected result:

$$x = \frac{4\,\mu g}{0.80} = 5\mu g/cm^2 \qquad \text{or} \qquad 4 \times 1.25 = 5\,\mu g/cm^2$$

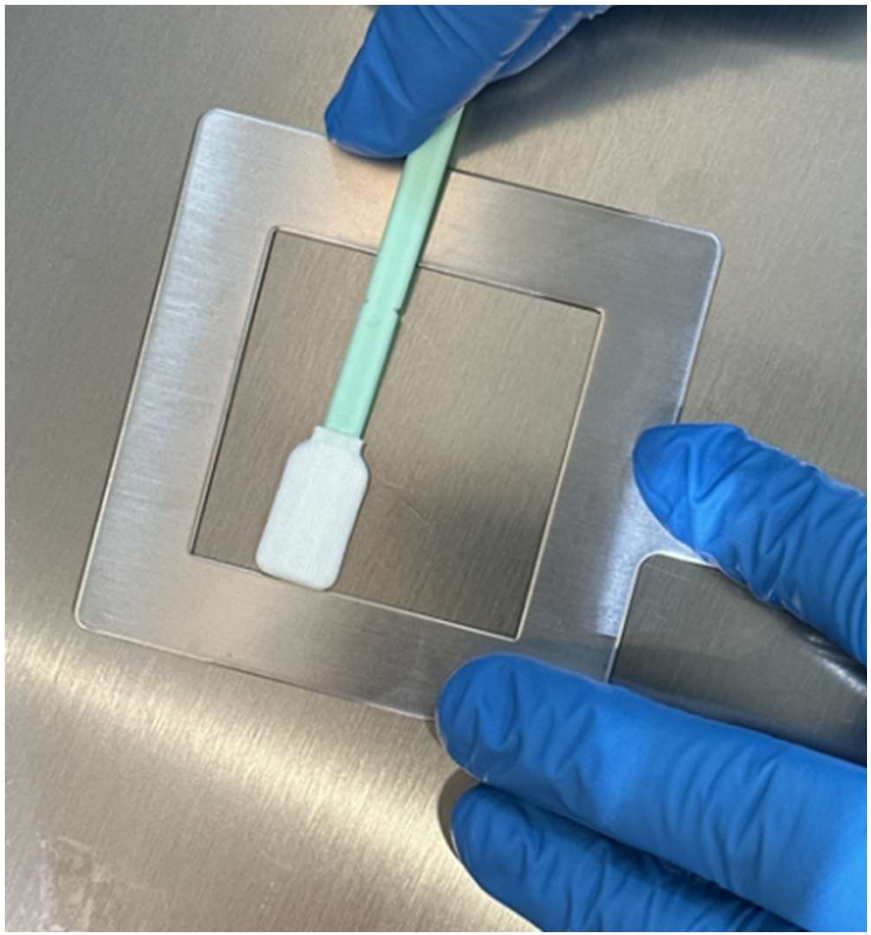
  - Although the laboratory measured 4 µg/cm², the estimated actual residue on the equipment surface is 5 µg/cm².
  - Rinse recovery calculation is essentially the same.
  - Low recoveries (<50-70%) may require justification
  - %RSD (reproducibility) should also be considered: ≤20% generally acceptable

TOC and Cleaning Validation – Background Correction

- **Correcting for TOC Background (Blank Correction)**
  - **Background TOC correction** is the process of accounting for organic carbon that comes from sources other than the residue being measured.
  - Since TOC analysis is non-specific, any carbon present in the sample contributes to the result.
  - **Sources of Background TOC**
    - Common sources include:
      - Purified water or WFI used for rinsing
      - Swab materials and extraction solvents
      - Sample containers and extraction vials
      - Environmental contamination (dust, fingerprints, airborne organics)
      - Instrument baseline noise



TOC and Cleaning Validation – Blank Correction



- **Why Background or Blank Correction Matters**
  - Suppose:
    - Final rinse TOC result = 250 ppb C
    - Rinse water blank = 50 ppb C
  - Without correction, it appears the equipment contributed 250 ppb carbon.
  - However:
    - Corrected TOC = 250 - 50 = 200 ppb C
    - Only 200 ppb C is attributable to equipment residue.
- **Blank Correction Formula**
  - Corrected TOC = Sample TOC - Blank TOC
  - Where:
    - Sample TOC = measured rinse or swab extract result
    - Blank TOC = TOC from water, swab, extraction solvent, or reagent blank

TOC and Cleaning Validation – Blank Correction

- **Example: Rinse Sampling**
  - Assume:
    - Acceptance limit = 500 ppb C
    - Purified water blank = 120 ppb C
    - Final rinse sample = 560 ppb C
  - Corrected result:
    - $560\ ppb - 120\ ppb = 440\ ppb$
    - Since:
      - $440\ ppb < 500\ ppb$
      - The equipment passes

- **Example: Swab Sampling**
  - Assume:
    - Swab blank = 25 ppb C
    - Extracted swab sample = 140 ppb C
  - Corrected value:
    - $140\ ppb - 25\ ppb = 115\ ppb$
      - The 25ppb contributed by the swab itself (would normally include the TOC contributed from the purified water and extraction vial) is removed from the reported result

TOC and Cleaning Validation – Blank Correction

- **Regulatory Perspective**
  - In cleaning validation, background/blank correction should be scientifically justified and consistently applied. The blank must:
    - Be measured using the same water, swabs, reagents, and containers used for sampling.
    - Be representative of the sampling process.
    - Remain stable and controlled during method validation.
  - During method validation many laboratories establish:
    - Instrument blanks
    - Reagent blanks
    - Swab blanks
    - Water system baseline TOC

TOC and Cleaning Validation – Blank Correction

- **Practical Consideration**
  - If background TOC becomes a large fraction of the acceptance limit, method sensitivity may be inadequate.
  - For example:
    - TOC acceptance limit = 100 ppb C
    - Water background = 80 ppb C
    - Only 20 ppb remains available for detecting residue. In this situation, you may need:
      - Lower-TOC rinse water
      - Cleaner sampling materials
      - A more sensitive TOC method
      - A product-specific assay (e.g., HPLC)

TOC and Cleaning Validation – Blank Correction

- **Typical Reporting Practice**
  - Many facilities report both:
    - Measured TOC: 250 ppb C
    - Blank TOC: 50 ppb C
    - Corrected TOC: 200 ppb C
  - This makes it clear how much carbon originated from the sampling system versus the equipment residue itself.
  - In pharmaceutical cleaning validation, effective background correction improves accuracy and prevents false failures caused by carbon originating from water, swabs, reagents, or the analytical system rather than from the manufacturing equipment.

TOC and Cleaning Validation – Blank Correction

Waters™

- **Method Validation Perspective**
  - A useful criteria is:

    $$\text{Blank TOC} + \text{Blank Variability} \ll \text{Acceptance Limit}$$

    For example:
    - Acceptance limit = 500 ppb C
    - Average blank = 40 ppb C
    - Blank SD = 5 ppb C
  - This is generally excellent because the blank is only 8% of the limit and highly reproducible.

    Conversely:
    - Acceptance limit = 150 ppb C
    - Average blank = 80 ppb C
    - Blank SD = 20 ppb C
  - This would be problematic because the blank is over 50% of the limit and exhibits substantial variability.

TOC and Cleaning Validation – Blank Correction

- **Background Limit Considerations**
  - There is no universal regulatory requirement for an "acceptable" blank TOC level in cleaning validation. Instead, the blank must be **low, stable, and insignificant relative to the cleaning validation acceptance limit**.
  - A common industry expectation is:
    - The blank should generally be **≤10–20% of the TOC acceptance limit**.
  - For example:

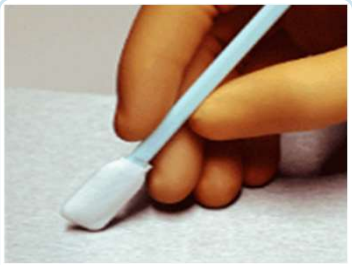
TOC Acceptance Limit	Preferred Blank TOC
500 ppb C	<50–100 ppb C
250 ppb C	<25–50 ppb C
100 ppb C	<10–20 ppb C

  - When the blank approaches 30–50% of the limit, the method becomes less reliable because small fluctuations in background carbon can significantly affect pass/fail decisions.

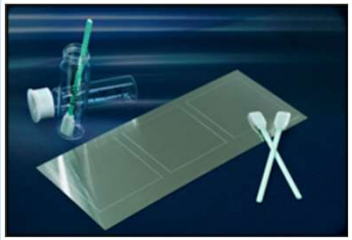
Waters ERA cleaning validation products

Products to support sampling, recovery studies, and routine cleaning validation workflows

Swabbing templates



Swabs



Swabs + coupon + vials

Coupons

Product lineup

How ERA helps labs build a complete cleaning validation workflow:

Swabbing templates

Certified templates define a known sample area so residue can be calculated consistently. #30032, #30029

Swabs

Low-TOC swabs support manual swab testing with broad solvent compatibility. #30033TX, #30031TX

Kits + vials

Bundled swab/vial kits help simplify workflows. #CV10005TX

Coupons

Custom glass, metal, and plastic surfaces for recovery studies and hard-to-swab areas.

Why ERA?

Custom options

to match customer surfaces

Traceability

CoAs for material and finish traceability for coupons

Quality and reliability

ISO 17025, ISO 17034 and ISO 9001 accredited

Technical support

for products + applications