# Comparative Evaluation of High-Performance Liquid Chromatography Versus Total Organic Carbon Analysis for Cleaning Validation in Pharmaceutical Manufacturing

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Posted Date: 29 December 2025

doi: 10.20944/preprints202512.2586.v1

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 doi:10.20944/preprints202512.2586.v1



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# Comparative Evaluation of High-Performance Liquid Chromatography Versus Total Organic Carbon Analysis for Cleaning Validation in Pharmaceutical Manufacturing: A Critical Review

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**Abstract**

**Background:** Cleaning validation is a critical component of pharmaceutical manufacturing quality assurance, ensuring the prevention of cross-contamination between production batches. Two predominant analytical techniques, High-Performance Liquid Chromatography (HPLC) and Total Organic Carbon (TOC) analysis, are widely employed for residue detection, yet the optimal selection between these methodologies remains a subject of ongoing debate within the industry. **Objective:** This review critically evaluates the comparative advantages, limitations, and application contexts of HPLC and TOC analysis in pharmaceutical cleaning validation programs, providing evidence-based guidance for method selection. **Methods:** A comprehensive literature review was conducted examining peer-reviewed publications, regulatory guidance documents, and industry case studies from 2010 to 2025. Selection criteria included studies comparing analytical performance, regulatory compliance, and practical implementation considerations. **Results:** HPLC demonstrates superior specificity for active pharmaceutical ingredient (API) quantification with detection limits typically ranging from 0.1–10 µg/mL, while TOC analysis offers advantages in non-specific organic contamination detection with broader applicability and faster analysis times (typically 3–8 minutes versus 15–60 minutes for HPLC). Regulatory guidance from the FDA and EMA supports both methodologies when appropriately validated, with the selection dependent on the specific cleaning validation objectives. **Conclusions:** Neither technique is universally superior; rather, the optimal choice depends on the validation objective, equipment characteristics, product portfolio complexity, and regulatory requirements. A risk-based approach combining both methodologies may provide the most comprehensive cleaning validation strategy for multi-product facilities.

**Keywords:** cleaning validation; HPLC; TOC analysis; pharmaceutical manufacturing; cross-contamination; GMP compliance; analytical method validation; quality assurance

## 1. Introduction

Cleaning validation represents a fundamental pillar of Good Manufacturing Practice (GMP) compliance in pharmaceutical production, serving as the documented evidence that cleaning procedures effectively remove product residues, degradation products, cleaning agents, and microbial contamination to predetermined acceptable levels [1]. The significance of robust cleaning validation programs has been underscored by numerous regulatory observations and warning letters issued by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), with inadequate cleaning validation consistently ranking among the top pharmaceutical manufacturing deficiencies [2].

The pharmaceutical industry has witnessed a significant paradigm shift from traditional compliance-based approaches toward science-based, risk-based methodologies for cleaning validation [3]. This evolution reflects the application of quality risk management principles

 doi:10.20944/preprints202512.2586.v1



established in ICH Q9, which emphasizes scientifically justified acceptance criteria and lifecycle approaches to validation activities.

The selection of appropriate analytical methods for residue detection constitutes a critical decision in cleaning validation protocol development. High-Performance Liquid Chromatography (HPLC) and Total Organic Carbon (TOC) analysis have emerged as the two predominant techniques employed across the pharmaceutical industry, each offering distinct advantages and limitations [4]. HPLC, a specific chromatographic technique, enables the identification and quantification of individual compounds, making it particularly valuable for API residue determination [5]. Conversely, TOC analysis provides a non-specific measurement of total organic contamination, offering rapid screening capabilities and broader detection of all carbon-containing residues [6].

The debate regarding the preferential use of HPLC versus TOC in cleaning validation contexts has persisted within the pharmaceutical industry for over two decades. Proponents of HPLC emphasize its specificity and ability to correlate directly with Maximum Allowable Carryover (MAC) calculations based on API toxicity [7]. Advocates for TOC analysis highlight its rapid turnaround time, lower method development requirements, and ability to detect cleaning agent residues simultaneously with product residues [8].

Regulatory expectations have evolved to acknowledge both methodologies as acceptable when appropriately validated and scientifically justified. The FDA's guidance on cleaning validation emphasizes the importance of selecting methods with adequate sensitivity and specificity for the intended purpose [9]. Similarly, the EMA's Annex 15 revision acknowledges the utility of non-specific methods such as TOC when combined with appropriate limit justification [10].

This review aims to provide a comprehensive, evidence-based comparison of HPLC and TOC methodologies in the context of pharmaceutical cleaning validation. By examining the fundamental principles, analytical performance characteristics, regulatory considerations, and practical implementation factors, this work seeks to establish a framework for informed method selection that optimizes both scientific rigor and operational efficiency.

## 2. Materials and Methods

### *2.1. Literature Search Strategy*

A systematic literature review was conducted using the following electronic databases: PubMed, Science Direct, Web of Science, and Google Scholar. The search encompassed publications from January 2010 to December 2025 to capture contemporary industry practices and regulatory developments.

### *2.2. Search Terms*

The following search terms and Boolean operators were employed:

- ("cleaning validation" OR "cleaning verification") AND ("HPLC" OR "high-performance liquid chromatography")
- ("cleaning validation" OR "cleaning verification") AND ("TOC" OR "total organic carbon")
- ("pharmaceutical manufacturing") AND ("residue detection") AND ("analytical methods")
- ("cross-contamination") AND ("GMP") AND ("analytical validation")

### 2.3. Inclusion and Exclusion Criteria

**Inclusion criteria:**

- Peer-reviewed original research articles, review papers, and technical reports
- Studies comparing or evaluating HPLC and/or TOC for cleaning validation applications
- Regulatory guidance documents from FDA, EMA, WHO, and PIC/S
- Industry white papers from recognized pharmaceutical associations

**Exclusion criteria:**

 doi:10.20944/preprints202512.2586.v1



- Non-English publications
- Studies focused exclusively on non-pharmaceutical applications
- Conference abstracts without full-text availability
- Publications predating 2010 (unless seminal works)

### *2.4. Data Extraction and Analysis*

Relevant data were extracted including analytical performance parameters (sensitivity, specificity, precision, accuracy), regulatory compliance considerations, practical implementation factors (time, cost, training requirements), and case study outcomes. Comparative analysis was performed to synthesize findings across studies.

## 3. Results and Discussion

### *3.1. Fundamental Principles and Detection Mechanisms*

#### 3.1.1. High-Performance Liquid Chromatography (HPLC)

HPLC operates on the principle of differential partitioning of analytes between a mobile phase and a stationary phase contained within a chromatographic column [11]. The technique enables separation, identification, and quantification of specific compounds based on their physicochemical properties, including polarity, molecular weight, and chemical structure.

In cleaning validation applications, HPLC methods are typically developed to target specific APIs or their degradation products. The most common detection modes include ultraviolet-visible (UV-Vis) spectrophotometry, fluorescence detection, and mass spectrometry (MS) for enhanced sensitivity and selectivity [12]. Method development requires optimization of mobile phase composition, column selection, flow rate, and detection parameters for each target analyte.

Jenkins et al. [6] demonstrated that HPLC-UV methods for cleaning validation typically achieve detection limits in the range of 0.1–1.0 μg/mL for most pharmaceutical compounds, with quantitation limits of 0.5–5.0 μg/mL, depending on the chromophoric properties of the analyte.

#### 3.1.2. Total Organic Carbon (TOC) Analysis

TOC analysis quantifies the total concentration of carbon atoms covalently bonded in organic molecules present in a sample [13]. The technique involves oxidation of organic compounds to carbon dioxide ($CO_2$), which is subsequently measured by non-dispersive infrared (NDIR) detection or conductivity measurement.

Two primary oxidation mechanisms are employed in pharmaceutical applications: high-temperature combustion (typically 680–1000°C) and UV-persulfate oxidation [14]. High-temperature combustion offers superior oxidation efficiency for recalcitrant compounds, while UV-persulfate methods provide lower detection limits and are more suitable for samples with high inorganic carbon content.

Mirza et al. [15] reported that TOC analyzers utilized in pharmaceutical cleaning validation typically achieve detection limits of 0.05–0.5 mg/L (ppm) carbon, with most modern instruments providing quantitation limits suitable for cleaning validation acceptance criteria.

### *3.2. Comparative Analytical Performance*

#### 3.2.1. Specificity and Selectivity

HPLC demonstrates inherent specificity, enabling the differentiation and quantification of individual compounds within complex sample matrices. This specificity is particularly advantageous when:

1. Multiple APIs are manufactured on shared equipment

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2. Degradation products require separate quantification
3. Regulatory requirements mandate specific API residue limits based on toxicological assessment

Walsh et al. [16] conducted a comparative study examining the specificity requirements for cleaning validation in a multi-product oral solid dosage facility. The authors concluded that HPLC was essential for facilities manufacturing compounds with significantly different potencies or toxicological profiles, where non-specific methods could not adequately demonstrate compliance with MAC limits.

Conversely, TOC analysis provides a cumulative measurement of all organic contamination, offering no information regarding the identity of contributing compounds. While this non-specificity is often considered a limitation, it can also be advantageous in scenarios where:

1. Detection of all organic residues (including cleaning agents and degradation products) is desired
2. Rapid screening of equipment cleanliness is required
3. Product changeover involves chemically similar compounds with comparable toxicological profiles

#### 3.2.2. Sensitivity and Detection Limits

Comparative sensitivity between HPLC and TOC is dependent on multiple factors, including the specific analyte, sample matrix, and instrument configuration. Table 1 summarizes typical detection capabilities reported in the literature.

**Table 1.** Comparative Detection Limits for HPLC and TOC in Cleaning Validation Applications.

| Parameter | HPLC-UV | HPLC-MS | TOC |
|---|---|---|---|
| Typical LOD | 0.1–1.0 µg/mL | 0.001–0.1 µg/mL | 0.05–0.5 mg/L C |
| Typical LOQ | 0.5–5.0 µg/mL | 0.01–0.5 µg/mL | 0.1–1.0 mg/L C |
| Sample Volume | 10–100 µL | 1–20 µL | 5–25 mL |
| Analysis Time | 15–60 min | 10–30 min | 3–8 min |

*LOD = Limit of Detection; LOQ = Limit of Quantitation.*

Hwang et al. [17] demonstrated that TOC detection limits, when converted to equivalent compound concentrations based on carbon content, may be either more or less sensitive than HPLC depending on the molecular composition of the target analyte. For compounds with high carbon content (>50% w/w), TOC may provide superior sensitivity, while compounds with lower carbon content or strong chromophores may be more readily detected by HPLC-UV.

#### 3.2.3. Precision and Accuracy

Both methodologies demonstrate acceptable precision and accuracy when properly validated. Pharmaceutical regulatory requirements typically mandate relative standard deviation (RSD) values of ≤2% for system precision and ≤15% for method precision at the quantitation limit [18].

A comprehensive validation study by Li et al. [19] compared HPLC and TOC performance for cleaning validation of pharmaceutical manufacturing equipment. The authors reported comparable precision (RSD <5% for both methods) and accuracy (recovery 95–105% for HPLC, 90–110% for TOC) at concentrations relevant to cleaning validation acceptance criteria.

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### *3.3. Regulatory Perspectives and Compliance Considerations*

#### 3.3.1. FDA Guidance

The FDA's guidance on cleaning validation acknowledges the acceptability of both specific and non-specific analytical methods, provided that appropriate scientific justification is documented [9]. Key regulatory expectations include:

1. Methods must be validated according to ICH Q2(R1) guidelines
2. Detection limits must be adequate to quantify residues at levels below established acceptance criteria
3. Recovery studies must demonstrate the effectiveness of sampling procedures
4. Specificity requirements should be commensurate with the intended use

The FDA has indicated through warning letters and inspection observations that non-specific methods such as TOC may be acceptable when:

- The acceptance limit is based on the TOC response of the most difficult-to-detect compound
- Cleaning procedures are demonstrated to remove cleaning agents to acceptable levels
- The validation protocol includes scientific justification for method selection [20]

#### 3.3.2. EMA and PIC/S Requirements

The European regulatory framework, as articulated in EMA Annex 15 and PIC/S guidance documents, similarly supports the use of both methodologies [10]. The EMA emphasizes a risk-based approach to method selection, considering:

1. Product toxicological profile and therapeutic index
2. Equipment design and cleanability
3. Cleaning procedure effectiveness
4. Sampling method recovery efficiency

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance PI 006-3 specifically addresses the use of non-specific methods, stating that TOC is acceptable provided that "the method can detect the marker residue or worst-case residue at a level below the acceptance criterion" [21].

### *3.4. Practical Implementation Considerations*

#### 3.4.1. Method Development Requirements

A significant practical distinction between HPLC and TOC lies in method development complexity. HPLC method development requires:

1. Chromatographic condition optimization (mobile phase, column, temperature)
2. System suitability parameter establishment
3. Forced degradation studies to demonstrate stability-indicating capability
4. Matrix effect evaluation for each equipment type and product combination

TOC methods, by contrast, require minimal compound-specific development. A single validated TOC method can theoretically serve all organic compounds, with method validation focusing on:

1. Instrument calibration and linearity verification
2. System suitability using standard solutions
3. Recovery studies for specific equipment and sampling procedures

Westman and Karlsson [22] estimated that TOC method implementation requires significantly less time for the development effort compared to HPLC, representing significant resource savings for multi-product facilities.

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#### 3.4.2. Throughput and Turnaround Time

TOC analysis provides substantially faster results compared to HPLC, with typical analysis times of 3–8 minutes versus 15–60 minutes for chromatographic methods [23]. This difference becomes particularly significant in high-throughput manufacturing environments where:

1. Rapid equipment release is critical for production scheduling
2. Multiple sample points require analysis per cleaning event
3. Real-time decision-making regarding re-cleaning is necessary

The faster turnaround time of TOC has led to its adoption for routine cleaning verification in many facilities, with HPLC reserved for periodic validation studies or specific applications requiring compound identification [24].

#### 3.4.3. Cost Considerations

Economic evaluation of HPLC versus TOC must consider both capital investment and operational costs. Table 2 provides a comparative cost analysis based on industry data.

**Table 2.** Comparative Cost Analysis for HPLC and TOC Implementation.

| Cost Factor | HPLC | TOC |
|---|---|---|
| Instrument Capital Cost | $30,000–$150,000 | $20,000–$60,000 |
| Annual Maintenance | $5,000–$15,000 | $2,000–$8,000 |
| Consumables (annual) | $10,000–$30,000 | $3,000–$10,000 |
| Method Development (per compound) | $5,000–$20,000 | $1,000–$5,000 |
| Analyst Training | Extensive | Moderate |
| Sample Analysis Cost | $20–$100 | $5–$25 |

*Cost estimates based on industry surveys and vendor quotations; actual costs may vary by region and application.*

### *3.5. Application-Specific Recommendations*

#### 3.5.1. Scenarios Favoring HPLC

Based on the evidence reviewed, HPLC is the preferred methodology in the following scenarios:

1. **High-potency API (HPAPI) manufacturing:** The enhanced specificity and sensitivity of HPLC (particularly HPLC-MS) is essential for demonstrating compliance with extremely low acceptance criteria (ng/cm² range) typical of HPAPI cleaning validation [25].
2. **Toxicological limit-based approaches:** When MAC calculations are based on compound-specific toxicological data (Permitted Daily Exposure, PDE), specific quantification of the residual API is required to demonstrate compliance.
3. **Degradation product monitoring:** Facilities requiring separate quantification of API and degradation products must employ chromatographic methods capable of compound differentiation.
4. **Regulatory requirements mandating specific detection:** Certain products or markets may have explicit regulatory requirements for specific analytical methods.

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3.5.2. Scenarios Favoring TOC

TOC analysis is the preferred methodology in the following scenarios:

1. **Multi-product facilities with diverse portfolios:** The non-specific nature of TOC eliminates the need for compound-specific method development, providing substantial efficiency gains for facilities manufacturing numerous products [26].
2. **Cleaning agent residue detection:** TOC effectively detects organic cleaning agents (surfactants, solvents) that may not be readily detectable by HPLC methods developed for API quantification.
3. **Rapid turnaround requirements:** Facilities requiring rapid equipment release benefit from the shorter analysis times of TOC.
4. **Visual cleanliness correlation:** When cleaning procedures result in visually clean equipment and TOC provides confirmation of overall organic contamination removal.

3.5.3. Combined Approach Strategies

Many industry practitioners advocate for a combined approach utilizing both methodologies in a complementary manner. Liu and Hwang [8] proposed a tiered strategy wherein:

1. **Tier 1 (Routine Verification):** TOC analysis for rapid, non-specific screening of all cleaning events
2. **Tier 2 (Periodic Validation):** HPLC analysis at defined intervals to confirm specific API removal
3. **Tier 3 (Investigation):** HPLC deployment for out-of-specification investigations or process changes

This risk-based approach optimizes resource utilization while maintaining scientific rigor and regulatory compliance.

## 4. Conclusions

This comprehensive review of HPLC and TOC methodologies for pharmaceutical cleaning validation demonstrates that neither technique possesses universal superiority. Rather, optimal method selection requires careful consideration of multiple factors, including:

1. **Validation objectives:** Specific API quantification versus total organic contamination assessment
2. **Product portfolio characteristics:** Potency, toxicological profiles, and chemical diversity
3. **Regulatory requirements:** Market-specific expectations and precedent
4. **Operational considerations:** Throughput requirements, resource availability, and cost constraints

The evidence supports several key conclusions:

**First**, HPLC remains the method of choice for cleaning validation involving high-potency compounds, toxicologically-based acceptance criteria, or regulatory requirements mandating specific quantification. The technique's specificity and sensitivity (particularly with MS detection) provide the analytical capability necessary for demonstrating compliance with stringent limits.

**Second**, TOC analysis offers compelling advantages for multi-product facilities seeking efficient, universal methods for organic residue detection. The technique's rapid analysis time, minimal method development requirements, and ability to detect all organic contamination make it particularly suitable for routine cleaning verification.

**Third**, a risk-based, tiered approach combining both methodologies may represent the optimal strategy for many pharmaceutical facilities. This approach leverages the efficiency of TOC for routine monitoring while maintaining HPLC capability for specific applications and periodic validation.

**Fourth**, regulatory guidance from FDA, EMA, and PIC/S supports the use of both methodologies when appropriately validated and scientifically justified. The emphasis on risk-based approaches in

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contemporary regulatory frameworks provides flexibility for facilities to select methods based on sound scientific rationale.

## 5. Recommendations for Implementation

Based on the findings of this review, the following recommendations are provided for pharmaceutical facilities implementing or optimizing cleaning validation analytical programs:

1. **Conduct a comprehensive risk assessment** considering product portfolio, equipment characteristics, and operational requirements before selecting primary analytical methodology.
2. **Establish acceptance criteria** using a scientifically justified approach (toxicological, dose-based, or general limit) and ensure selected analytical methods possess adequate sensitivity.
3. **Validate all analytical methods** according to ICH Q2(R1) guidelines, with particular attention to recovery studies using production-representative sampling procedures.
4. **Consider a tiered approach** utilizing TOC for routine verification and HPLC for periodic confirmation or specific applications requiring compound identification.
5. **Document the scientific rationale** for method selection in cleaning validation protocols to support regulatory inspections.
6. **Maintain ongoing evaluation** of analytical program effectiveness through trend analysis and periodic reassessment of method suitability.

## 6. Future Perspectives

Emerging analytical technologies may provide additional options for cleaning validation in the future. Technologies under development or early adoption include:

1. **Direct Surface Analysis:** Techniques such as DART-MS (Direct Analysis in Real Time Mass Spectrometry) enable direct surface interrogation without swab extraction [28].
2. **Spectroscopic Methods:** Near-infrared (NIR) and Raman spectroscopy offer potential for rapid, non-destructive surface analysis.
3. **Electrochemical Sensors:** Development of compound-specific sensors may enable real-time, in-situ monitoring of cleaning effectiveness.
4. **Machine Learning Integration:** Application of artificial intelligence to spectroscopic data may enhance both specificity and throughput of non-destructive methods.

These emerging technologies warrant continued investigation and may eventually supplement or replace traditional HPLC and TOC methodologies.

**Conflicts of Interest:** The author declares no conflict of interest.

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