

**Title:** Alternative Analytical Method Validation in Pharmaceuticals: Replacing a Regulatory Analytical Method in Cleaning Validation

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This re-titled poster is replacing:

Alternative Analytical Method Validation in Pharmaceuticals: Real World Examples of Why Some Regulatory Analytical Methods Should be Replaced

**Introduction:**

Results obtained from analytical instrumentation in the pharmaceutical industry undergo intense scrutiny because they are quite often used to make decisions that ultimately ensure the health and safety of consumers. Whether it be data from research and development, manufacturing or quality control, the accuracy and precision of laboratory and process analytical instrumentation is of paramount importance in validating data for use in all levels of decision making within a pharmaceutical facility. The scientific details of instrument validation for the pharmaceutical industry are available in guidance documents on the topic of analytical procedures and methods validation. This discussion focuses on a critical subset of the topic referred to as regulatory and alternative analytical procedure relationships, specifically as it applies to the analytical instrumentation used in cleaning validation.<sup>1</sup>

Regulatory and Alternative Analytical Procedures are defined as follows<sup>2</sup>:

*Regulatory Analytical Procedure* – The analytical procedure being used to evaluate a defined characteristic of a drug substance or drug product.

*Alternative Analytical Procedure* – An analytical procedure proposed by an applicant for use in place of the regulatory analytical procedure.

**Background:**

It was the infamous 1988 recall of Cholestyramine Resin USP that set into motion the rigorously scientific approach to cleaning validation and verification the pharmaceutical industry employs today. Reflecting back to the introduction of the Food and Drug Administration's (FDA's) "Guide to Inspections Validation of Cleaning Processes", a reference document for FDA personnel, it is clear that a paradigm shift was taking place with respect to the science of cleaning validation. Standard practice in the industry today is the establishment of acceptable residue limits (or carry-over limits) for all drugs manufactured in a facility. Today these residue limits are very thoughtfully derived from the toxicology and efficacy knowledge gained during drug developments and clinical trials, but it was not so long ago that cleaning verifications involved little more than organoleptic inspections of manufacturing equipment, with no monitoring of cleaning programs to meet strict residue limit criteria. Along with the emergence of these scientifically-based limits came a need to both effectively sample process equipment and also accurately obtain results from analytical instrumentation so that accurate

determinations of cleanliness can be made. Liquid Chromatography (LC) was one of the first techniques employed in cleaning validation sample analysis not simply because of its qualitative and quantitative capabilities, but even more likely because of its widespread use throughout the industry.<sup>3,4</sup>

### **Discussion:**

The use of LC for the analysis of cleaning validation/verification samples remains the most common even today, but that truth stems mainly from its practical implementation into the application some twenty years ago. LC's versatility, and the sound understanding that industry and agency scientists shared of its theory and operation made it a logical choice.

As cleaning validation knowledge and experience has increased in recent years, new technologies for sample analysis have emerged that offer improved performance characteristics over HPLC. Total Organic Carbon (TOC) analysis is one analytical method that has significant advantages as compared to HPLC, and it is being employed in cleaning validation applications in increasing numbers of late. The detection limits of TOC, its accuracy and precision capabilities and most importantly its non-specific nature make it a much more powerful tool than HPLC for cleaning validation. Non-specificity, although questioned by some as appropriate, allows TOC users to screen for contamination outside active ingredients and detergents with every analysis; something chromatographic techniques often fail to offer. Even with this knowledge, change has been slow to take place for a number of reasons, not the least of which has been the absence of a simple migration path for those facilities already having validated HPLC for use in their cleaning validation/verification.<sup>5,6,7</sup>

The FDA states that there are essentially four criteria you must consider carefully before implementing an analytical procedure for a cleaning validation application. They are:<sup>8</sup>

Sensitivity - It is necessary to demonstrate that the method is appropriate for the established contamination limits with respect to sensitivity and limits of detection.

Practicality - The method should be practical and rapid, and whenever possible, it is desirable to utilize previously existing equipment (that is well-known/understood both by the user and the FDA).

Validation Scheme - The method shall be such that it can be readily validated in accordance with regulatory requirements (FDA, ICH, etc.) for instrumentation.

Successful Recovery Study - The analytical development shall include compound recovery studies that challenge the sampling and testing methods.

It is typically accepted that the following details be included in the description of analytical procedures used in pharmaceutical manufacturing<sup>3</sup>:

Principle – A description of the basic principles of the analytical procedure should be given here (separation, detection, etc.).

Sampling – Justification for selection of sample types, numbers and analysis criteria.

Reagents – Detailed list of reagents, their preparations, associated hazards and directions for use.

System Suitability Testing – Ensuring a properly functioning analytical system, suitability standard testing parameters and associated acceptance criteria should be discussed. Confirms the system will produce reliable results independent of environmental conditions.

Preparation of Standards – Procedures for the preparation and use of all standard solutions (calibration, internal, stock, verification, working, etc.).

Sample Preparation – Sample preparations for individual sample tests should be detailed.

Procedures – Full description of the analytical procedure should be provided.

Calculations – Representative calculations, including mathematical transformations or formulas included in data analysis and reporting must be included.

Reporting of Results – Complete formatting details for report, including, but not limited to retention times, detection limits and quantitation limits. May include information for both drug products and impurities.

## TOC Method Validation

The TOC method validation section of your documentation should include the following validation characteristics for the method you have developed<sup>2</sup>:

- Accuracy – The measure of exactness of an analytical method, or the closeness of agreement between the value which is accepted either as a conventional, true value or an accepted reference value and the value found.
- Precision – Precision is the measure of the degree of repeatability of an analytical method under normal operation and is normally expressed as the percent relative standard deviation for a statistically significant number of samples.
- Detection Limit – The point at which instrument response for an analyte or compound (carbon concentration) can be distinguished from instrument noise, but not be accurately quantitated.
- Quantitation Limit – The lowest concentration of carbon that can be determined with acceptable precision and accuracy under the stated operational conditions of the method.
- Linearity – Linearity should be demonstrated by an r-squared value indicating that the regression line will be an excellent predictor when transforming sample data.
- Range – Details of the instrument's analytical range, including relevant method modifications necessary to achieve.
- Robustness – Ability of the analytical procedure to remain unaffected by small but deliberate variations in method parameters.

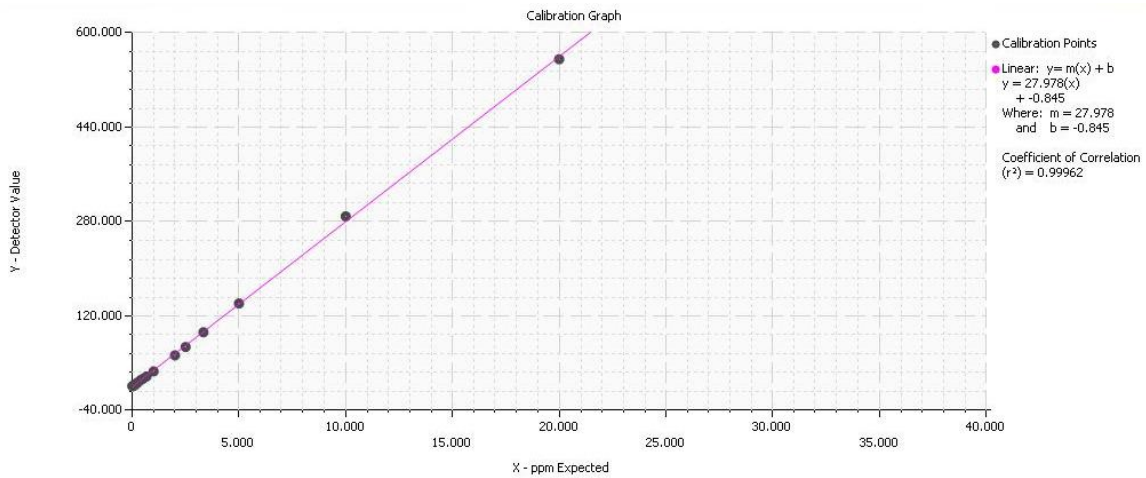
The sensitivity of some TOC instruments makes them a perfect fit for cleaning validation analysis. Data from Table 1 indicates that the sensitivity of the technique is more than adequate to qualify it for use in cleaning validation applications. These detection limits

are arguably more impressive than chromatographic methods when you consider the breadth of analysis as far as potential contamination types.

Sample	Result (ppm C n= 9)	Std. Dev. (+/- ppm C)	MDL (ppm C)	LOQ (ppm C)
Purified Water	0.0021	0.0006	0.0017	0.0060

Table 1 - Data obtained using Tekmar Fusion TOC Analyzer.

Linearity over a range of TOC values appropriate for established limits should be demonstrated. With coefficients of correlations > 0.995 generally deemed acceptable, TOC analyzers can achieve acceptable linearity over rather wide ranges. The  $r^2$  value of 0.9996 for TOC concentrations from 0-20 ppm shown in Graph 1 support excellent linearity.



Graph 1 – Linearity data from 0-20 ppm TOC obtained using Tekmar Fusion TOC Analyzer.

Concentration (ppm C)	Result (ppm C n= 3)	Std. Dev. (+/- ppm C)	RSD	Dilution	Min / Max Criteria (ppmC) (85 - 115% dev)
0.005	0.0046 (PASS)	0.0017	N/A	1:200	.0043 / .0058
0.01	0.0095 (PASS)	0.0021	N/A	1:100	.0085 / .0115
0.013	0.0126 (PASS)	0.0004	2.88%	1:75	.0113 / .0153
0.02	0.0172 (PASS)	0.0008	4.90%	1:50	.0170 / .0230
0.025	0.0224 (PASS)	0.002	9.00%	1:40	.0213 / .0288
0.04	0.0349 (PASS)	0.0013	3.64%	1:25	.0340 / .0460
0.05	0.0468 (PASS)	0.003	6.44%	1:20	.0425 / .0575
0.067	0.0608 (PASS)	0.0026	4.22%	1:15	.0567 / .0767
0.1	0.0939 (PASS)	0.0013	1.39%	1:10	.0850 / .1150
0.2	0.1957 (PASS)	0.0024	1.25%	1:5	.1700 / .2300
0.25	0.2439 (PASS)	0.0021	0.87%	1:4	.2125 / .2875
0.333	0.3294 (PASS)	0.0038	1.16%	1:3	.2833 / .3833
0.5	0.5074 (PASS)	0.0024	0.47%	1:2	.4250 / .5750

Table 2 – Auto-Check Standard Data diluted from 1 ppmC KHP TOC Stock Standard for 13 points (n=3 replicates per standard) automatically using the Tekmar Fusion TOC Analyzer.

Selection of recovery data for compounds used in manufacturing by several manufacturers shows that the obligation to demonstrate successful product recoveries is met, with values ranging from 89%-108% (Table 2). FDA, WHO and general industry criteria range from 50%-80% for what are considered acceptable levels.<sup>4,9</sup>

Compound	Molecular Weight	Carbon % (e -estimate)	Carbon in Standard (ppm)	Measured Carbon by TOC (ppm)	Percent Recovery (%)
Bovine IgG	14.50 kDa	51 e	1.0	1.11	108
Trypsin Inhibitor	21.50 kDa	49 e	1.0	0.87	89
L-Glutamic Acid	147.13 g/mol	40.81	1.0	1.04	104
L-Tryptophan	204.23	64.69	1.0	1.09	109
Citric Acid	192.13	37.50	1.0	1.03	103

Table 3 - Data obtained using Phoenix 8000 TOC Analyzer.

### Conclusion:

The advantages of TOC for cleaning validation use are many, yet most labs find themselves in the position of already having a validated regulatory analytical procedure in place. Defending a change to an alternative analytical procedure like TOC doesn't need to be a daunting task and should require no more than two weeks as far as data

collection. Following the requirements detailed in regulatory guidelines for analytical instrument qualification and method validation is all that is necessary to be able to confidently defend your decision to change. Remember that one of the most important attributes of TOC that should be detailed in a discussion of analysis principles is its non-specific nature and inherent ability to detect and quantify contamination that chromatographic methods may not.

**References:**

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9. WHO Guide to Good Manufacturing Practices, Part 2 – Validation, WHO/VSQ/97.02.