GE
Water & Process Technologies
Analytical Instruments

Application Note

The Advantages of TOC Analysis Over HPLC for Cleaning Validation

Part 1 of 2

Advances in technologies and mounting manufacturing costs are leading the global pharmaceutical industry to evaluate alternate means to enable greater efficiency and productivity. In this highly competitive industry, it is vital to ensure the highest possible drug quality while eliminating high production costs and unnecessarily lengthy validation work. Interest in Total Organic Carbon (TOC) analysis as a non-specific method for cleaning validation has grown considerably during the past seven years because specific analytical testing like High Performance Liquid Chromatography (HPLC) has proven to be a bottleneck in the cleaning validation process, significantly contributing to equipment downtime after cleaning.

This application note is presented in two parts and investigates the advantages of using a non-specific method for cleaning validation over more traditional analytical methods. The intent of this application note is to present the value proposition of TOC and to help pharmaceutical manufacturers realize increased resource productivity, yield improvements, equipment downtime reduction, and improved bottom lines. Part 2 takes a closer look at TOC methods and identifies why Sievers* TOC technology is well suited to cleaning validation applications.

Why TOC for Cleaning Validation

An increasing number of companies are utilizing TOC analysis for cleaning validation because it is faster, easier, and more economical than other analytical methods. The TOC method yields high sample throughput and reduces cleaning validation protocol execution time. This is true even with compounds generally thought to be insoluble in water or with bulky proteins common in the biotechnology industry. Furthermore, the FDA accepts the TOC method[1] in its regulatory guidelines for measuring contaminant residues.

During a cleaning validation study it is often necessary to establish acceptance criteria limits based upon more than one target residue or compound. HPLC is limited in that it can determine only one residue for one individual given assay. In cleaning validation, multiple compounds would thus require multiple analytical tests. With these multiple tests, unanticipated contaminants or cleaning agents could potentially be overlooked and unknown peaks could show up on the chromatograph. TOC will detect more than one target compound given it is a non-specific method.

Key Weaknesses of HPLC: Ghost Peaks, Regulatory Scrutiny, and Costly Maintenance

Due to long setup and analysis times, HPLC often contributes one to two days of production downtime before processing equipment can be certified for cleanliness. Unknown peaks and costly maintenance have been the root cause of this downtime. Additionally, HPLC is the most commonly cited analytical method in warning letters issued by the FDA after pharmaceutical facility inspections. Recent warning letter statements referencing HPLC address insufficient detection, failure to identify unknown peaks, failure to calibrate instruments prior to use, lack of linearity testing, instrument accuracy, and failure to perform system suitability prior to analysis.[2]

Insufficient training or qualifications for lab personnel running HPLC instruments is also scrutinized heavily. A recent Warning Letter stated "...procedures for conducting HPLC testing are inadequate because sample run times and retention times...have not been established in your approved test methods. Our investigator found that your laboratory employees routinely stop chromatographic runs immediately after the active peak has eluted, and as a result, any peak that elutes after the active peak will not be detected."[3]

This heightened regulatory scrutiny shows that the FDA is aware of HPLC's disadvantages. This awareness is further indicated in the FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories: "Sometimes the company's employees have insufficient training or time to recognize situations that require further investigation and explanation. Instead they accept unexplained peaks in chromatograms with no effort to identify them."[4]

It is no secret that performing HPLC analysis for cleaning validation involves some level of uncertainty. Unknown peaks, also known as "ghost peaks," contribute to this uncertainty, resulting in lengthy troubleshooting time and failed validation operations. Peaks from previous injections, contamination, bubbles, column fouling, worn-out guard columns, and trace contaminants or cleaning agents in the sample are some of the contributing factors that lead to costly replacement of parts on the HPLC unit. For example worn polymeric fittings or tubing and a contaminated guard column affect peak shape and require replacement. Depending upon the peak shape distortion, guard columns may require weekly or even daily replacement, greatly increasing unplanned maintenance costs.

Cost of Ownership

In general, the average capital cost of a TOC analyzer is 37% lower than that of an HPLC instrument. Most pharmaceutical facilities have a TOC analyzer in place for USP water release purposes. The same analyzer can serve both USP and cleaning validation functions, potentially eliminating the need for a capital purchase entirely. Additionally, operating costs for TOC analysis are 40 to 80% less than the cost of a HPLC instrument. This does not account for the additional time required for frequent maintenance, removing contaminates by reconditioning the column, using well-degassed solvents, daily column equilibration, and daily calibration of the detector. Operational costs for HPLC will increase due to unreliable components and the multiple external parts needed to run the instrument effectively.

Associated Production Downtime Costs with HPLC

The "downtime calculator" shown in **Table 1** compares production downtime costs associated with the analytical methods most commonly used in the pharmaceutical industry for cleaning validation. The downtime calculator demonstrates the use of HPLC and TOC in a pharmaceutical company that is producing a "blockbuster" therapeutic with 24/7 315 days of production.[5] Annual gross revenues for the product are referenced to be $2.5 billion, with 750 resources contributing to the production of the drug product. By using TOC for cleaning validation, the pharmaceutical manufacturer can reduce production downtime costs by 97%.

Ease of Use for a Non-Specific Method

An HPLC operation requires attended sample analysis and specially trained personnel. TOC analysis requires no special training and reduces the analytical method development time by 60%. The use of TOC also reduces the end user decision points, eliminating downtime and human error and streamlining the cleaning validation or verification process. Documentation for TOC analysis is simplified to ensure compliance and promote real-time documentation, thus facilitating rapid approval of lab results for the staged equipment. This allows for quick equipment turnaround time, which is crucial for pharmaceutical manufacturing.

Table 1. Downtime Calculator

	HPLC	TOC	Factors and Assumptions
Corporate Hourly Cost Calculations			
(the value of one hour's time to the organization)			
Annual Gross Revenues of Product	$ 2,500,000,000.00	$ 2,500,000,000.00	Assuming Novel/Blockbuster Product
Divided by Total Production Hours	**7560**	**7560**	Assuming 315 Production Days 24/7 Coverage
Equals Hourly Corporate Contribution	$ 330,687.83	$ 330,687.83	
Employee Downtime			
(the average value of one hour of an employees time to an organization)			
Hourly Corporate Contribution	$ 330,687.83	$ 330,687.83	
Divided by Number of Employees at Facility	750	750	# of People contributing to the process
Equals Hourly Employee Contribution	$ 440.92	$ 440.92	
Downtime Due to Equipment Not Released			
(the average time the equipment is tied up by any contributing factors)			
People Hours Required to Troubleshoot/Operate Instrumen	16.75	0.75	
Times the Average Hourly Employee Contribution	$ 440.92	$ 440.92	
Equals **Production** Downtime Costs	$ 7,385.36	$ 330.69	
Employee Downtime Costs			
(the incremental costs related to the company waiting for operations to get back on schedule)			
Hours the production equipment is down	25.75	0.75	
Times the Average Hourly Corporate Contribution	$ 330,687.83	$ 330,687.83	
Equals **Employee** downtime costs	$ 8,515,211.64	$ 248,015.87	
Total Costs of Downtime	**$ 8,522,597.00**	**$ 248,346.56**	

Table 2. Swab Recoveries[6]

Active	Solubility Per Merck Index	Actual Solubility	Solubility as TOC	Recovery HPLC	Recovery TOC
Sulfacetamide	Sparingly Soluble	>10,000 ppm	>5,000 ppm	91.0%	93.1%
Sulfabenzamide	Substantially Insoluble	300 ppm	127 ppm	71.2%	78.0%
Sulfathiazole	Substantially Insoluble	600 ppm	254 ppm	82.4%	86.5%

Percent Recovery of Insoluble Organics

With the use of a non-specific method it has been argued that using TOC for cleaning validation did not provide good percent recoveries during cleaning validation studies of insoluble organics. Some argue that achieving greater that 50% recovery with a non-specific method analyzing an insoluble compound is very unlikely. **Table 2** demonstrates the swab percent recoveries of three "insoluble compounds" comparing HPLC to TOC. The TOC recovery is from coupons spiked at 4 µg/cm^2 or approximately 2 parts per million (ppm) in 20 mL of water and demonstrate that the response efficiency is well above 50%.[6]

Part 2 Contents

Part 2 of this application note explores TOC technology offerings, and identifies differentiating factors to consider when evaluating TOC for cleaning validation.

References

[1] FDA Website: www.fda.gov/cder/guidance/cGMPs/equipment.htm#TOC.
[2] "The Gold Sheet." FDC Reports, March 2005.
[3] FDA Website: www.accessdata.fda.gov/scripts/wlcfm/index-date.cfm
[4] FDA Guidance Document: Guide to Inspections of Pharmaceutical Quality Control Laboratories
[5] This assumes a production shut down for routine maintenance on manufacturing equipment
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