GE
Water & Process Technologies
Analytical Instruments

Application Note

PAT Application: At-Line TOC for Cleaning Validation and Product Changeover

The Versatility of the Sievers 900 Portable TOC Analyzer Provides Users Ultimate Efficiency Gains in Cleaning Validation and Product Changeover

Since the introduction in 2004 of the *Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Develop-ment, Manufacturing, and Quality Assurance*, tools have been available to the pharmaceutical industry to help reach the desired state of quality. The above-mentioned guidance document provides a scientific, risk-based framework, intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency.

Part of this innovation involves obtaining data from the process by means of an "at-line" method, e.g. a Total Organic Carbon (TOC) measurement of a sample that has been taken close to the process stream. This application note demonstrates the applicability and capability of at-line TOC analysis for periodic swab sampling for Cleaning Validation and applying the same practices for Product Changeover utilizing the Sievers* 900 Portable TOC Analyzer. This application note also demonstrates the versatility of the 900 Portable and provides examples of how TOC measurement was used to increase efficiency and to ensure that there are no significant changes occurring during the cleaning and product changeover processes. In addition, this application note also provides an example of the At-Line TOC Process Analytical Technology (PAT) application.

Incorporating a Portable TOC Analyzer in Validation Documentation

The effort to implement At-Line TOC for Cleaning Validation was undertaken at a major pharmaceutical company in 2006 (referred to as Company Q for reasons of confidentiality). Once the validation master plan was outlined, worst-case conditions selected, and acceptance criteria justified, validation protocols and reports were generated to validate TOC for cleaning validation utilizing the protocol templates and reports available in the Sievers Cleaning Validation Support Package. The validation documentation and analytical results indicated that TOC methodology (Sievers UV persulfate, membrane-conductometric) was suitable and recovered the challenge components during the analytical method validation and qualification process. Also, the TOC instrumentation was specifically classified as a portable analyzer, being utilized at various locations within the manufacturing facility. Sievers Certified System Suitability Standards were used and system suitability testing was performed pre- and post-sampling.

Using TOC for Periodic Monitoring (Cleaning Verification) and Product Changeover

Within the protocol report, the direct (swab) sampling method was performed on a periodic basis and whenever product changeover was occurring. Acceptance criteria were validated and established for both sampling methods, swab and indirect (rinse), to be 1.25 ppm C. Even though robust validation studies demonstrated successful results, areas were selected to demonstrate worst-case challenges and therefore would be periodically monitored with swab sampling and TOC analysis. The following diagram demonstrates four "worst-case" or challenging locations on a GE Healthcare large-scale Chromaflow chromatography column.

The protocol indicated that a Water for Injection (WFI) rinse be performed after the swabbing samples have been taken to provide assurance that the system is clean and that the swabbing process did not contaminate the system or piece of equipment. After the swab samples were taken, the Sievers 900 Portable TOC Analyzer was then moved to the location of the CIP skid to analyze the WFI rinse. During this final rinse cycle, a TOC rinse sample was taken to again show that that there were no trace sampling materials (contamination) left in the system.

PAT—At-Line TOC Analysis: How it was Achieved

The sample preparation for the swabs and the rinse sample occurred in the laboratory along with system suitability testing. After passing the system suitability test, LIMS (Laboratory Information Management System) numbers were assigned to the TOC samples. The samples were labeled with the defined swabbing areas, and documented appropriately in a lab notebook or equipment use record. The sampling materials and the TOC analyzer were carried out to the production floor, where the sampling occurred at-line following a CIP of the column. Once the swabs samples were obtained and parts reconnected, the TOC analysis was started via the 900 Portable's integrated online sampler (iOS). Results from the analysis were documented in the lab notebook and appropriate changeover documentation. Once the TOC analysis of the swabs was complete, a WFI rinse was initiated and a rinse sample was collected at an appropriate time as described in relevant procedures. The rinse sample was collected and analyzed at-line with the Sievers 900 Portable TOC Analyzer to ensure no trace material from the swabs or environment contaminated the equipment. Table 1 provides an example of the thorough documentation that was generated.

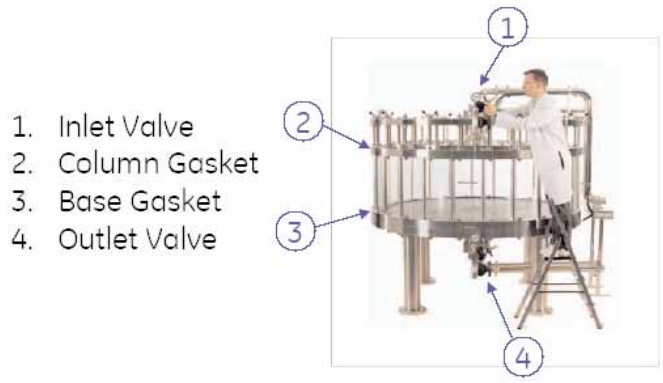

Figure 1. Purification Column

Table 1. Example of Documentation

Analyzer	Standards	Lot Info & Exp. Date	Response Efficiency 85-115%	Pass/Fail*
Sievers 900P #12313	Sievers Standard Set	Rw: Lot 05516 Exp. 06/21/2006 Rs: Lot 05516 Exp. 06/21/2006 Rss: Lot 05516 Exp. 06/21/2006	99%	Pass
Equipment Swab Location	**LIMS Number**	**Swab Number**	**TOC Result TOC < 1.25 ppm C**	**Pass/Fail***
Inlet Valve	120231	1	126 ppb	Pass
Column Gasket	120232	2	222 ppb	Pass
Base Gasket	120233	3	245 ppb	Pass
Outlet Valve	120234	4	134 ppb	Pass
Cleaning Circuit	**LIMS Number**	**Water Grade**	**TOC Result TOC < 1.25 ppm C**	**Pass/Fail***
Column 1_A	120235	WFI Final Rinse	42.3 ppb	Pass
Analyzer	**Standards**	**Lot Info & Exp. Date**	**Response Efficiency 85-115%**	**Pass/Fail***
Sievers 900P #12313	Sievers Standard Set	Rw: Lot 05517 Exp. 09/21/2006 Rs: Lot 05517 Exp. 09/21/2006 Rss: Lot 05517 Exp. 09/21/2006	98%	Pass

**If a deviation or TOC failure occurred, the changeover or periodic monitoring procedure required an incident report to be generated and the LIMS number be documented in the lab notebook and equipment use record.*

Streamlining the Process with Quality

This example is one of many in utilizing innovative instruments for PAT applications. Typically, product changeover or the periodic monitoring samples can be completed within minutes or hours utilizing the Sievers 900 Portable TOC Analyzer, providing efficiency gains for single or multi-product facilities. The simple approach shows a potential cost savings opportunity for product changeover methods but does not impact the analytical laboratory performing routine water sampling or additional cleaning validation TOC sampling. Quality and manufacturing groups are able to document the results in real-time, and sign-off validation packages and product changeover records quickly with a high level of confidence that the equipment is clean and ready for the next product to be manufactured.

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[1] "Guidance for Industry PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," 2004. http://www.fda.gov/cder/OPS/PAT.htm.

[2] Large-scale Chromaflow chromatography column reproduced with kind permission of GE Healthcare Bio-Sciences AB.

[3] Documentation tables like this can be found in the Sievers Cleaning Validation Support Package. For more information please visit www.geinstruments.com.

USA
GE Analytical Instruments
6060 Spine Road
Boulder, CO 80301-3687 USA
T +1 800 255 6964 or +1 303 444 2009
F +1 303 444 9543
geai@ge.com
www.geinstruments.com

Europe
Unit 3 Mercury Way
Urmston, Manchester, M41 7LY
United Kingdom
T +44 (0) 161 866 9337
F +44 (0) 161 866 9630
generaluk.instruments@ge.com

300 00133 Rev A
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