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## HYDE HIGHLIGHTS

### Just published

Implementation of the ASTM Standard for Manufacturing Systems Verification Peter Watler, BioProcess International, Vol. 9, No. 8, September 2011, pp. 24–33

### ISPE National Conference

[Meet the Hyde team at table #409](#) in Dallas, Texas November 6-9, 2011 .

### November 22-23

Berlin, Germany - Keith Bader presents: "Translating the new process validation paradigm to cleaning processes" at the inaugural [Informa Lifesciences event](#)

## Process Analytical Technology (PAT) for Enhanced Verification of Bioprocess System Cleaning

By Keith Bader, Director of Technical Quality

In the manufacture of therapeutic as well as biocommodity products, contamination control is of paramount importance to product quality, patient safety, and GMP compliance. Equipment cleaning is the primary line of defense in preventing adulteration from contaminants. Yet the control and monitoring of effective cleaning processes can be difficult. A recent survey found that 60 percent of FDA warning letters cited 21 CFR 211.67 (equipment cleaning and maintenance) deficiencies relating to inadequate equipment cleaning procedures, monitoring, and documentation (European Compliance Academy, 2006).

### PAT Approaches for Monitoring Cleaning Effectiveness

Traditionally, monitoring cleaning processes' critical quality attributes (CQAs) involves multiple orthogonal off-line analytical measurements. Today, online PATs enable assessment cleaning processes and an understanding "such that quality is controlled and assured throughout production" (Watts, 2006).

Flow rate may be monitored as a critical quality attribute as it relates to the application of external energy (or turbulence). With an understanding of the equipment design, the control system can be programmed to not only monitor flow rate, but to calculate a Reynolds number,

$$Re = \left( \frac{\rho u D}{\mu} \right)$$

for each portion of the equipment, thereby returning a parameter value more relevant to the cleaning process than flow rate alone. This allows active control of the cleaning cycle, which in turn enables maintenance of a turbulent flow regime throughout the cleaning circuit by adjusting the CIP supply flow rate.

### Online TOC Analysis for Monitoring System Cleaning

The cleaning process must not only be highly effective in removing process contaminants, it must also include rigorous methods for assessing the efficacy of the cleaning processes. By demonstrating the absence of carbonaceous residues in rinse water, TOC (total organic carbon) analysis is an effective PAT for evaluating the efficacy of the cleaning processes. Unfortunately, some online TOC technologies that perform destructive analyses on a captive sample can take from 1 to 5 minutes before the results are available. Such delays make

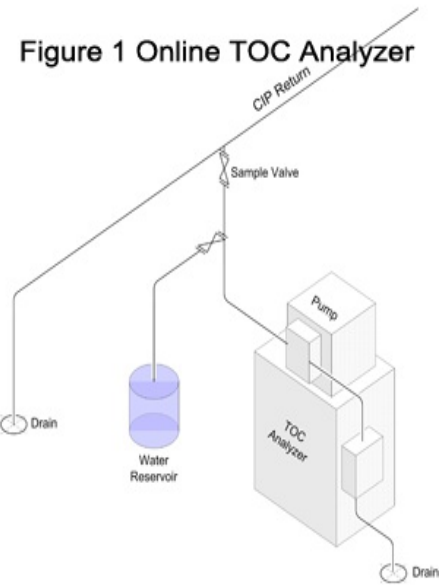




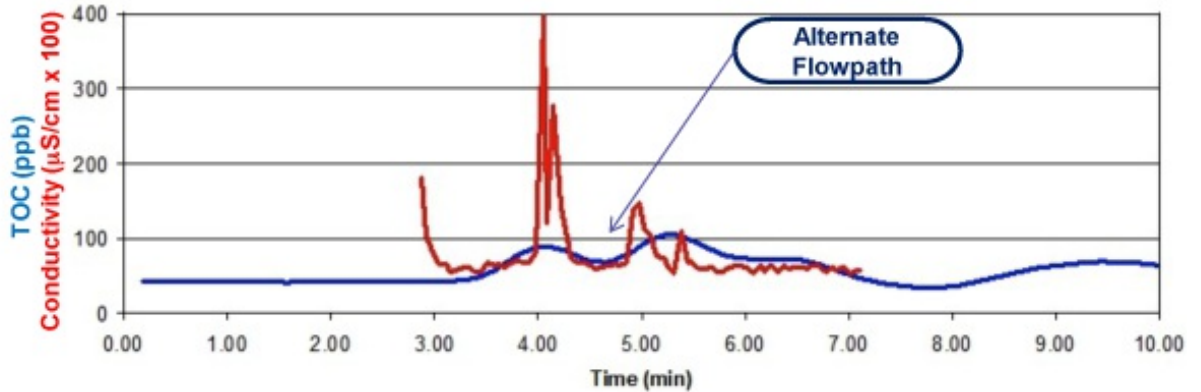
them impractical for real-time process control.

To obtain accurate results in CIP PAT applications, the online analyzer must not be confounded by interference from ionic species, variations in sample pressure, or changes in sample temperature. Membrane conductometric detectors prevent such confusion by allowing selective permeability of CO<sub>2</sub> across a membrane. The measured conductivity thus results entirely from inorganic carbon (IC) and total carbon (TC), effectively eliminating interference from conductive ionic species. Figure 1 shows the configuration of an online TOC analyzer installed on the return line of an educator-assisted CIP skid.

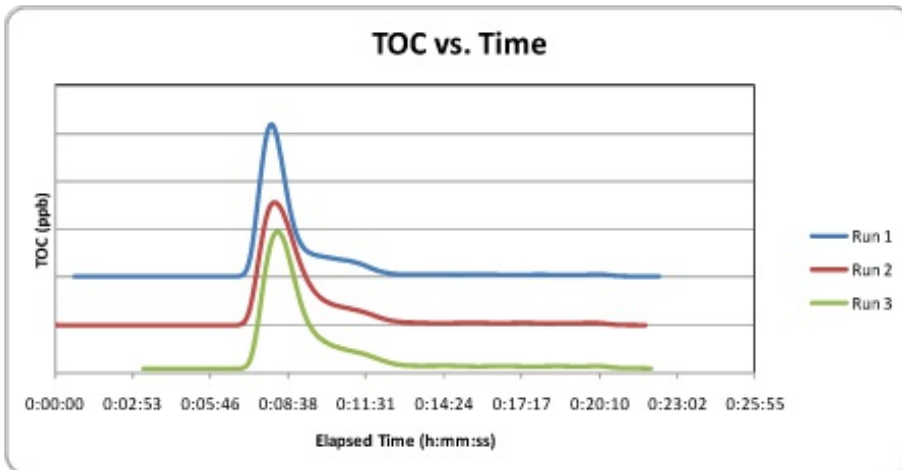
Analyzing the rinsate using this system provides cleaning washout kinetics for optimization as well as consistency. The shape of the final rinse concentration profile relays information about the cleaning circuit from which the information was collected. The rinse profile shows two distinct peaks. The second peak is a result of final rinse water being redirected through an alternate flow path on a bioreactor cleaning circuit. With each increase in TOC, there is also an increase in solution conductivity, indicating that the rise in TOC is likely a result of the surfactants in the formulated cleaning agent employed for the chemical wash, rather than from residual production residues.



**Bioreactor CIP**  
Conductivity / TOC Overlay vs. Time



Similarly, examination of the concentration profiles over time can reveal consistency from run to run. Overlaying the three profiles provides a process “fingerprint” showing that the general shape and magnitude of each peak is very similar.



Advances in both sensor technology and automation have combined to provide a heightened level of monitoring and confirmation of equipment cleaning processes. These monitoring tools include online sensing of flow rate, temperature, TOC, conductivity, and pressure drop. The benefits of employing these tools include demonstrating



control and consistency of cleaning processes and providing greater assurance of adequate cleaning prior to equipment reuse. These online PATs can also enable cleaning fingerprints that are unique to each system and demonstrate cleaning consistency that would not be possible with a simple point sample. Employing PAT will improve cGMP compliance by serving as a useful tool to satisfy the Stage 3—Continued Process Verification expectations of the FDA’s process validation guidance (FDA, 2011).

*More information can be found in the forthcoming publication: “PAT Applied in Biopharmaceutical Process Development and Manufacturing: An Enabling Tool for Quality-by-Design (Biotechnology and Bioprocessing)”, Eds: Cenk Undey, Duncan Low, Jose C. Menezes, Mel Koch (Editor)*

## Experts Ask Experts

*A Facility Engineer asks:*

We are replacing some of our legacy process tanks so that they can be more consistently and easily cleaned. What should I look for when selecting a hygienic design for a bottom-mounted mixer and how would I clean it?

*Keith Bader, Principal Engineer, answers:*

The chief advantage of a bottom-mounted mixer is that it doesn’t have a mechanical seal and sterile boundary to worry about. Here at Hyde, we’ve conducted studies to evaluate mixers and found that they all performed more or less equivalently provided that general hygienic design principles were incorporated. The critical elements to look for are:

- An open head design
- Surfaces sloped for drainability
- A means for flushing the annular space between the shaft and the mixer body

As for cleaning, the manufacturer may recommend cleaning by immersion, which can lead to quiescent or laminar flow in the bottom of the vessel, possibly extending the required cleaning time. With open head designs, I recommend the use of a custom fixed spray device that directs a stream towards the open center port in the mixer to flush the annular space between the head and the shaft. The mixer should be rotated slowly during the cleaning process to aid in the distribution of cleaning solutions.

Maintaining fluid in the annular space allows the mixer to be run without damage that would otherwise result from being run dry while flushing any residual material. Since the bearing surfaces are lubricated by cleaning solutions, the agitator does not need to be submerged, so the CIP cycle for the tank can be run with a minimal heel of water. Consider the design of the raceway or bearing surface on which the mixer head rotates. The design should allow for this area to be easily flushed during cleaning.



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