

This article offers an alternative method to cleaning validation using online total organic carbon analyzers to determine cleaning validation in-situ. Methods are compared with traditional laboratory analysis.

Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management

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One Total Organic Carbon (TOC) analysis has progressed significantly in the past few years, yet it remains an under-utilized technology. The US FDA has stated that TOC is an acceptable method for both cleaning validation and routine monitoring, provided the suitability of the method has been established and documented.¹ Advances in TOC analyzer oxidation and analysis methodologies make their integration into Clean-in-Place (CIP) systems instrumentation relatively easy as a means to provide near real time cleaning process performance information. While it is currently possible and practical to utilize online TOC analysis for the real-time assessment of CIP cycle performance, the biopharmaceutical manufacturing industry has been slow to adopt it without favorable and accepted regulatory precedents. However, these precedents do exist in FDA guidance documents on Process Analytical Technology (PAT), the Risk-Based Manufacture of Pharmaceutical Products (both in 2004), and the International Conference on Harmonization (ICH) Quality Risk Management guideline in 2005, which signal a regulatory environment receptive to active monitoring and control of critical process parameters.

The case study presented in this article was conducted to test the relative cleanability of three different bottom mounted agitators. The data by which the cleaning process was evaluated was acquired using an online TOC analyzer integrated into the return line of a CIP system as well as by conventional manual indirect and direct sampling and offline analysis.

Implementing TOC as an online process analytical technology requires first determin-

ing if the analytical technology and method are appropriate for the application. Primarily, the installation of process analyzers on equipment used in GMP manufacturing facilities should be done only after risk analyses are performed to ensure that the installation does not adversely affect the process or product quality. The location, physical integration, and automation of the online analyzer into the cleaning system return piping are important considerations as these factors may impact the accuracy and robustness of the measurements. Once installed, the reliability of the technology must be demonstrated through a comparison of online results with existing conventional test methods, including any developmental studies supporting the efficacy and appropriateness of the particular analytical method. In this case, the analytical method TOC, is used to detect process and product residues in final rinse water following cleaning.

Selection of a TOC Analyzer Based on Instrumental Characteristics and CIP Process Considerations

The selection of an appropriate TOC analyzer requires knowledge of its basic operating principles to ensure that CIP process conditions do not interfere with analytical results. Since there is little opportunity to customize the available features of an online TOC analyzer, selection of an analyzer with the appropriate oxidation and sensor equipment can accommodate both analyzer specifications and CIP operational requirements. Though the basic operational principles for all TOC analyzers are much the same, the oxidation and sensor technologies vary between manufacturers. Matching the character-

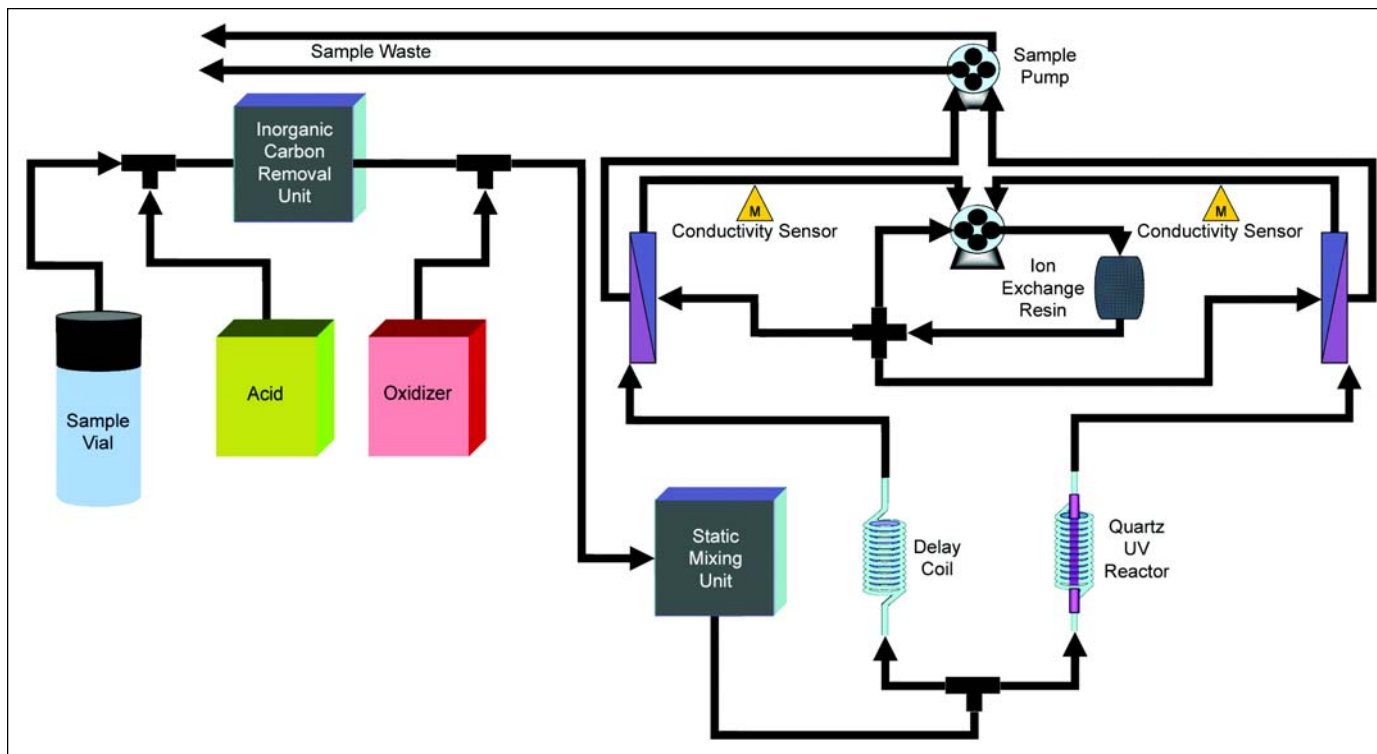


Figure 1. Diagram of a membrane conductometric UV/persulfate TOC analyzer - optional inorganic carbon removal units may be employed if samples have higher levels of dissolved atmospheric CO₂.

istics of CIP processes with an array of specific sensor and oxidation technologies compatible with those characteristics will yield a robust application of the online analyzer, enabling minimized operational and validation efforts with respect to cleaning processes.

For CIP applications, accurate results from an online analyzer must not be confounded by interference from ionic species, variations in sample pressure, or changes in sample temperature. Since conductivity is used in some cases to quantify evolved CO₂, the ionic species in many cleaning agent formulations must be considered as a potential source of interference. These conductive species may be addressed through the use of a membrane conductometric sensor as in Figure 1 or through the use of photometric detection schemes that are insensitive to the presence of conductive ions. Membrane conductometric detectors allow selective permeability of CO₂ across a membrane without permitting other conductive ions into the measurement zone. Therefore, measured conductivity results entirely from Inorganic Carbon (IC) or Total Carbon (TC) oxidized to CO₂, effectively eliminating this source of interference.

For online TOC analyzers in which samples are directly introduced to the analyzer from the CIP return manifold, sample temperature and pressure are relevant parameters to consider. Sufficient pressure is required in the sample line to ensure that the analyzed sample concentration doesn't significantly lag in the CIP return piping. Additionally, care also should be taken to protect the analyzer from pressures exceeding manufacturer's recommendations. In most cases, CIP pressures will not exceed the pressure specifications for an instrument; however, close attention must still be given to

the configuration, size, and placement of automated sampling valves and associated sample lines drawing from CIP system return lines. Stabilization of analyzer inlet pressure and flowrate will allow for consistency in the residence time of fluid in the sample lines.

Temperature fluctuations are a relevant concern depending on the selected analyzer, especially if the analysis method is conductometric. Conductivity is a temperature dependant measurement that each instrument manufacturer accommodates in a different manner. Temperature variations in the sample stream may be addressed through temperature compensated conductivity sensors, or measurement of raw conductivity data with sampling apparatus that allow for temperature equilibration through ambient dissipation or active heat exchange. Alternatively, a detection method that is not temperature dependant (such as NDIR) may be used.

TOC concentration is indirectly obtained by calculating the difference between two directly measured parameters; TC and IC. Equation 1 illustrates this relationship.

$$TOC = TC - IC \quad (Eq 1)$$

Total Carbon is determined by oxidizing organic carbon containing compounds to CO₂ and quantifying both the inorganic carbon already present in the sample along with the evolved CO₂. In the case of a membrane conductometric analyzer (Figure 1), Inorganic Carbon (IC) in analyzed samples results from dissolved CO₂ species (HCO₃⁻, CO₃²⁻), and may be measured directly without oxidation of the sample.

As depicted in Figure 1, solution from the sample vial is injected into the analyzer where acid is introduced to the

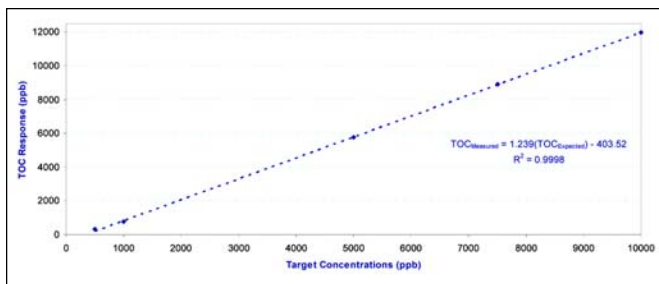
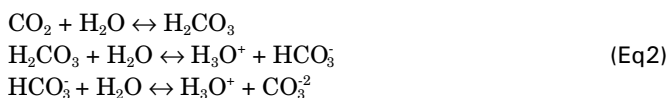


Figure 2. TOC response curve for Bovine Serum Albumin.

sample stream. The added acid shifts the equilibrium such that inorganic carbon species convert to CO_2 . After the acid addition, a persulfate oxidant is added and the sample stream mixed to ensure homogeneity. The sample stream is then split with one stream passing through a reactor and exposed to UV light, initiating a photolysis reaction. As the sample in the reactor is oxidized, CO_2 evolves and is transferred across a gas permeable membrane into a deionized water stream where its conductivity is measured. The formation of the conductive species occurs via the carbonate buffer pathway shown in Equation 2.



The other sample stream flows through a hydro-dynamically identical path (identified in Figure 1 as the delay coil) where dissolved CO_2 is transferred across the membrane and conductivity is measured to provide an inorganic carbon reference measurement required for the calculation of TOC.

Analytical and Sampling Method Development

For this study, two analyzers were employed; both equipped with membrane conductometric sensors. The offline analyzer used a methodology based upon UV and persulfate oxidation, whereas the online analyzer used only UV oxidation. To ensure the reliability and comparability of the measurements from the online and offline analyzers, USP system suitability tests were performed to confirm response efficiency using 1,4 benzoquinone and sucrose standards. The instrumental limit of detection of 50 ppb TOC required per the USP² was met for both analyzers.

Sampling Technician	Sample ID	Positive Control TOC (ppb)	Blank Corrected Sample TOC (ppb)	Percent Recovery	Sampler LOD	Sampler LOQ
1	250	231	181	78.5	125	377
	500	633	594	93.8		
	1000	1137	1016	89.3		
2	250	231	194	84.1	122	371
	500	633	561	88.5		
	1000	1137	936	82.3		
3	250	280	193	68.8	195	589
	500	808	649	80.2		
	1000	1105	1017	92.0		

Table A. Surface swab recovery results.

Once operation of both analyzers was demonstrated to be acceptable, methods were developed using the offline analyzer to characterize the Bovine Serum Albumin (BSA) to be used as a representative process soil and to evaluate and quantify the systemic and experimental error associated with TOC surface swab sampling. Stainless steel coupons also were spiked at multiple weight loadings to develop a recovery response curve.

From a 10% by weight solution of BSA, a series of dilutions were prepared with target concentrations of 500, 1000, 5000, 7500, and 10,000 ppb TOC. The solutions were then analyzed to ensure that the TOC response curve for BSA was linear and to empirically characterize the samples' carbon content to establish a correlation between the concentrations of TOC and BSA.

Analysis of the samples produced the response curve shown in Figure 2. Also reported are the linear regression trend line through the data points, which provides an indication of the linearity of the relationship, Limits of Detection (LOD) and Limits of Quantitation (LOQ). The regression line correlation coefficient (R^2) of 0.9998 demonstrates that the regression line fits the data and is a reasonable model for the plotted data.

To ascertain the surface swab recovery characteristics for BSA, a study was conducted using stainless steel coupons spiked with known concentrations of BSA. The target organic carbon loading (ppb) is indicated by the Sample ID numbers in Table A. To account for the inter-individual variability, the study was conducted with three technicians independently executing the swab sampling method. Swab sampling recovery was evaluated by comparing the TOC recovered from the coupons to the TOC content of positive control samples in which equivalent amounts of BSA solution to that spiked on the surface of the corresponding coupons was spiked into a vial containing 40mL of diluent. The results are summarized in Table A, and shown graphically in Figure 3 and Figure 4.

The correlation coefficient (R^2) value greater than 0.99 for each of the technicians provides assurance that the recovery fits a linear model when inter-individual variability is taken into account. Evaluation of the LOD and LOQ for the sampling method for each technician is shown in Table A and ranges from 122 to 195 ppb TOC, and 371 to 589 ppb TOC, respectively. The slope of each recovery curve also is a representation of the overall surface swab recovery over the

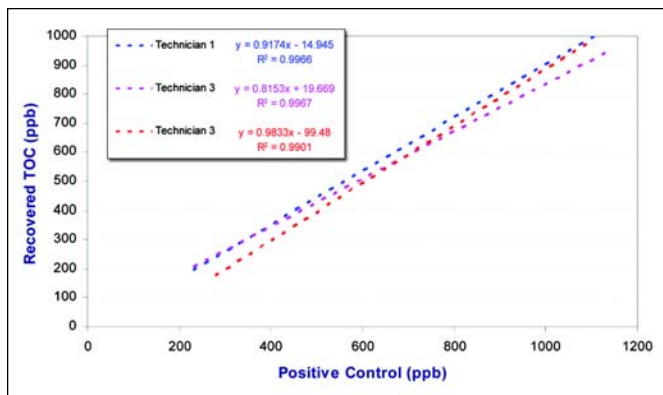


Figure 3. Individual technician swab recovery results.

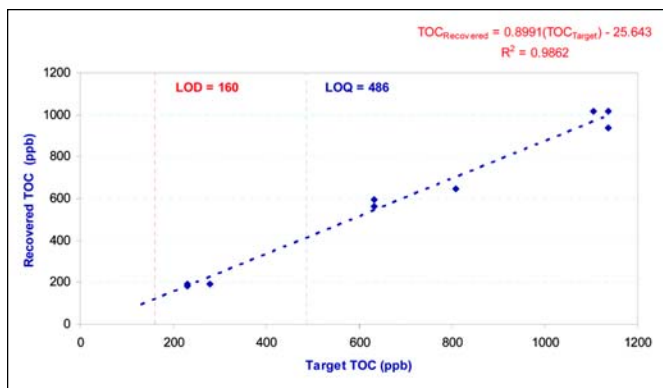


Figure 4. Characterization of TOC surface swab sampling method (BSA swab recovery [aggregate]).

Sampling Method	LOD(ppb TOC)	LOQ(ppb TOC)
Swab	161	486

Table B. Sampling method limits.

range of the indication that on average, each of the technicians will, at a minimum, likely recover greater than 80% of BSA residues remaining on process surfaces within the tested range.

The slope of each line shown in Figure 3 indicates the overall recovery across several residue loadings for each technician. Additionally, relative standard deviation of the individual recovery results was used as the primary statistic of interest to assess the precision of the results and the reliability of the data for each individual technician. Reviewing the discrete relative standard deviation numbers and the R^2 values for each technician, some variability is expected and was apparent.

Intuitively, pooling the data for all of the technicians should create a model incorporating inherent systemic error as well as that resulting from inter-individual variability. To confirm this hypothesis, a t-test conducted for the three data sets confirms that the sample sets for all the technicians may be pooled since they are statistically similar with a high probability of sharing the same sample mean.

Linear regression statistics for the response curve, as well as LOD and LOQ were determined. The LOD and LOQ are evaluated through the following equations:

$$LOD = \frac{3.3s}{m} \quad (\text{Eq3})$$

$$LOQ = \frac{10s}{m} \quad (\text{Eq4})$$

In Equations 3 and 4 above, s defines the standard deviation from the calibration curve and m the slope of the regression line.³ However, the quantity, s , may be determined multiple ways: from the standard deviation of the regression line, the standard deviation of y-intercepts of the regression line, and the standard deviation of an appropriate number of blank responses.

The pooled data for all the technicians is represented graphically in Figure 4, and shows an overall recovery of approximately 90% with a correlation coefficient of 0.986, and aggregate limits of detection and quantitation of 160 and 486 ppb TOC.

As noted above, an alternative method for estimating the LOD is to use the average of the swab results from the swabbing of 10 clean stainless steel coupons. This will quantify the approximate background levels resulting from the water, vials, swabs, and other random experimental sources. The average TOC from the swabbing of 10 clean stainless steel coupons was 161 ppb with a relative standard deviation of 9.3%. Accordingly, the LOD values determined by the two methods were nearly identical.

Using TOC swab LOQ as the limit for passing cleaning results, values in excess the TOC swab LOD were evaluated to determine a root cause for the failure. Corroboration of the online and offline rinse samples also was considered in the analysis.

Cleaning Study Results

The CIP test system depicted in Figure 5 was used to compare the cleanability of three bottom mounted agitators of differing design. The components that comprise the CIP test system include a water supply tank, a heat exchanger, automated valves, Variable Frequency Drive (VFD) controlled pumps,

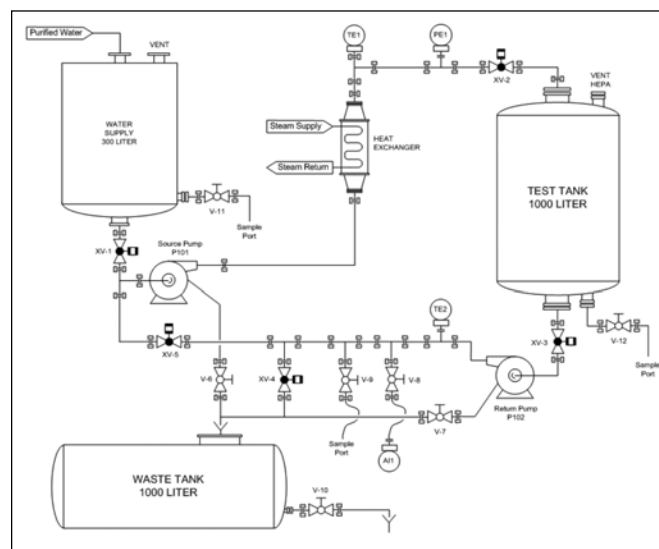


Figure 5. Schematic of CIP skid with online TOC analyzer.

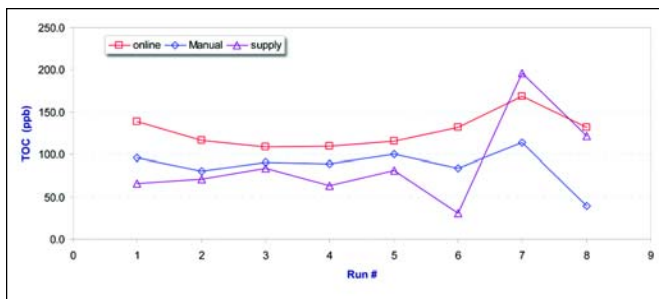


Figure 6. Comparison of manual and online TOC rinse samples.

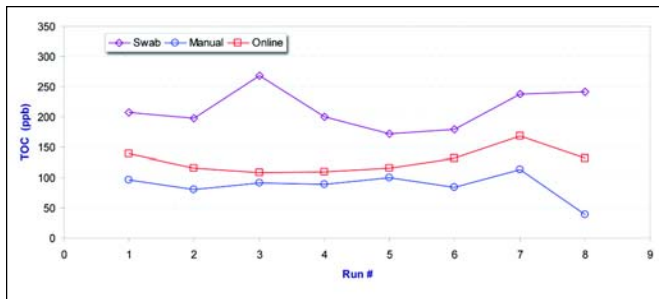


Figure 7. Comparison of online to direct and indirect sampling method results.

and a 1000L vessel in which the agitators were installed for testing. The critical parameters of temperature and flow rate were controlled via PID controllers, along with carefully controlled circuit fill volumes and detergent concentrations to ensure uniform reproducible operations for each run.

To assess each run, final rinse water samples were taken online through the TOC analyzer sample line located at valve V-8. The TOC analyzer is represented in the drawing as analog input signal AI-1. All manual samples taken for comparison were drawn from valve V-9, which was located immediately adjacent to the TOC analyzer sample line. To provide a point of reference for each run, the supply water was manually sampled from V-11. The agitators were each installed in the tank in analogous positions and, as noted before, subjected to the same cleaning procedure and parameters.

To soil the equipment, BSA was manually applied to the internal tank surfaces as well as the entirety of each agitator and allowed to dry. Once dry, the CIP cycle was initiated, consisting of an initial rinse, an alkaline wash, an intermediate rinse, an acidified wash, and purified water final rinses. For each cycle, Steris CIP-100, at 1% concentration by volume, was the cleaning agent used for the alkaline wash. The cleaning agent used for the acidic wash solution was 1% by weight phosphoric acid. The acid wash cycle was then followed by a once-through rinse and a subsequent recirculated rinse. Since the online analyzer required a brief equilibration period before it was ready to sample, the second final rinse was recirculated as once-through rinse durations were inadequate for the analyzer to complete its start up cycle.

Just before completion of the cleaning cycle, manual samples were taken at the beginning of the final rinse recirculation. After completion of the cleaning cycle, manually acquired rinse and swab samples were taken for compari-

son with those from the online TOC analyzer.

Comparability of the sampling and analytical methods was assessed through analysis of the manual and the online results. These data are shown in Figure 6. The online results also were compared to TOC surface swab samples to any correlation between the methods.

Correlation of the results of all three methods is apparent with the most notable event being the results from run 7. The supply water was accidentally contaminated by overfilling the flat topped supply tank, transferring contaminants from the lid and seal of the vessel into the bulk solution. In each case, the sampling methods detected the excursion.

The comparative results for the surface swab samples are shown in Figure 7. The general trend is the same for the surface swab samples with the exception of run 3 in which the surface swab results are higher than either the manual or online rinse samples. This may have been due to inadequate surface cleaning of BSA residue that was not completely soluble in the final rinse water.

The data from all runs demonstrates that rinse samples, whether online or manual, do provide a good indication of the residue levels on the equipment surfaces with the absolute TOC value difference between swab and rinse samples being attributed to the added TOC background inherent to the swabbing method.

Another interesting observation is the fact that the manually collected rinse sample TOC results were lower than those from the online analyzer, while one might expect quite the opposite. The manual samples were taken at the beginning of the recirculated rinse cycle prior to an extended recirculation time. Once the analyzer had completed the initial rinse cycle (approximately 4 ½ minutes), the online samples were taken. The higher results from online TOC samples may be due to the recirculation of the rinse water prior to sampling. Recirculation of final rinse water is a deviation from typical CIP processes, and recirculation causes the rinse water to be directed back through pathways that would not ordinarily have contact with a final once-through rinse. This potentially contributed some TOC to the final rinse results from the additional surface area contacted by the final rinse water.

Another contributing factor to the higher online TOC results is the configuration of the online analyzer sampling piping which is depicted in Figure 8. The illustration approximates the spatial layout of the sampling equipment. The TOC analyzer sample valve, XV-8, was oriented downward, and did not have an additional drain or flush valve to remove solution from the lines. The manual rinse sampling valve, on the other hand, was flushed prior to sample collection per the procedure for the sampling method, clearing any residue from the sample path that could contribute to elevated TOC levels.

This principle of rinsing the path prior to sample collection and analysis may be incorporated into the sampling arrangement for the analyzer to allow for clearance of residues prior to sample collection. An example of a possible piping configuration to minimize process residue retention is shown in Figure 9. In this arrangement, the sample line branches from the process line such that the inlet to the line is constantly

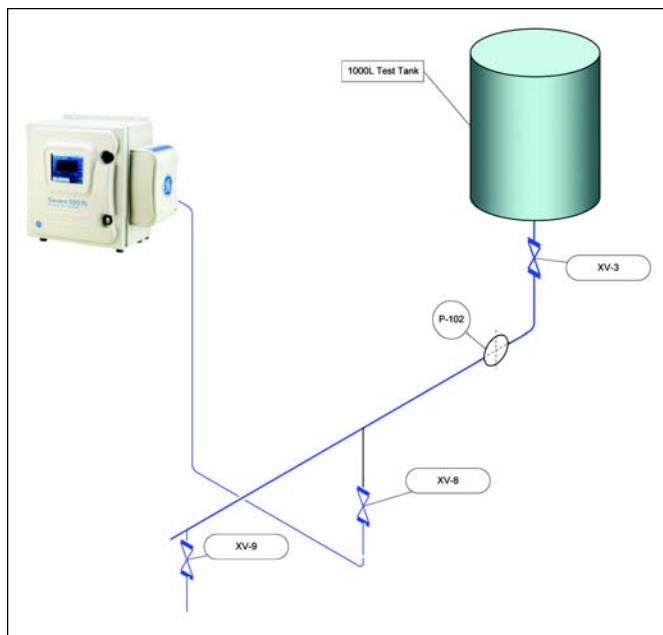


Figure 8. Isometric layout of sampling equipment.

swept clear by the process fluid. Further, the installation of a drain valve is useful to allow for flushing of the line prior to sampling, as well as draining the sample line after sampling is completed. Sloping the sample line back to the drain valve also will minimize retention of process fluid from previous sampling operations.

Conclusions

The cleaning of pharmaceutical manufacturing equipment systems by automated Clean-in-Place (CIP) means has long provided superior reliability and consistency as compared to manual cleaning operations that are subject to human error. Through the introduction of more reliable and affordable sensor technologies, including advances in online TOC technology, the cleaning process can be very effectively controlled and monitored by removing variability inherent to manual collection and analysis of cleaning verification and validation samples. Accordingly, implementation of TOC as a process analytical technology for cleaning systems can improve knowledge and control of the cleaning process beyond real time

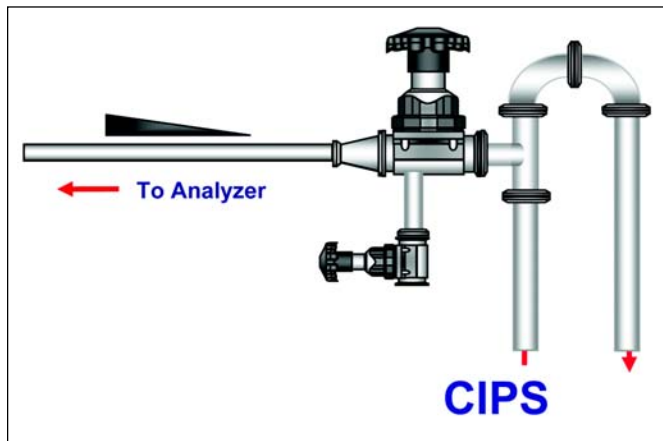


Figure 9. Online analyzer sampling configuration.

awareness of final rinse water quality at a discrete moment in time. The combination of online TOC and online conductivity measurements provides a means for real-time verification of cleaning cycle performance, and using statistical process control methodologies, ongoing analysis of the consistency of critical control parameters and quality attributes for the cleaning process. This ongoing monitoring can provide the basis for evaluating drift and the need for re-qualification based upon events rather than elapsed time. The data from ongoing monitoring also can provide a foundation for cleaning validation that is not based upon a model of three passing commercial scale runs, but rather a model that uses evidence from cleaning cycle performance, on an every run basis, to provide assurance of successful operations prior to the manufacture of each production run.

The implementation of online TOC sampling and analysis must be done by carefully selecting an analyzer that is compatible with the cleaning process and subsequently installing it such that the results are truly representative of TOC levels in final rinse streams. The selected TOC analyzer must be able to tolerate conductive ions such as those present in cleaning agents. The analyzer also must be able to tolerate, and depending on the intended use, analyze occasional spikes of TOC greater than 1 – 2 ppm. This study has demonstrated that an advanced oxidation differential conductivity membrane sensor based instrument is suitable for online CIP rinse water analysis. Other technologies may be suitable based on the specific requirements of the application. If the analyzer will not be used for an application in which conductive ions are present and TOC concentrations are rarely in excess of 2 ppm, it may be possible to use an advanced oxidation based instrument that measures TOC through the use of direct conductivity. For concentrations of TOC in excess of 2 ppm with the possibility of conductive ions, end users may wish to consider the use of a UV persulfate oxidation system with an NDIR or differential membrane conductivity sensor.

Additionally, the sample equipment on the CIP system should be configured to deliver solution to the analyzer quickly without carryover from run to run. This is best accomplished by ensuring a short residence time with adequate turbulence in fully drainable sample lines for complete removal of fluid when the equipment is not in use. Once qualified, the TOC analyzer can identify trends predictive of adverse events or inadequate process control, allowing for timely application of corrective measures. This utilization of real time cleaning process performance information will yield product quality and economic benefits.

To gain regulatory acceptance for the utilization of online TOC analysis for ongoing monitoring of cleaning efficacy, the instrumentation and method must be qualified in a manner consistent with offline validated and compendial sampling and analytical methods. Further, implementation of online TOC sampling and analysis as a component of a PAT strategy for cleaning processes is only practical if the results are equivalent or better than those attained from existing methods. This may be done by comparing the results obtained

using both methods and modifying the sampling equipment configuration to ensure that the online methodology is accurate and robust, and at the very least, equivalent to the results of offline sampling methods.

Although some have suggested that online TOC measurement provides additional liability should TOC levels exceed acceptance limits in final rinse water, online TOC measurement compliments and enhances the level of process knowledge from which critical process decisions may be made. Typically, once a system has been validated, TOC rinse samples are not taken for every run unless necessitated by poor system performance or a philosophy that embraces an extremely low risk tolerance. CIP systems often rely on monitoring and control of critical process control parameters, measured by temperature, flow rate, and conductivity sensors in the appropriate locations¹² to ensure that cleaning cycles operate within established and validated ranges. While this approach effectively takes care of the input side of the cleaning process, final rinse water TOC, which is a critical quality attribute for cleaning, has not typically been addressed. Online final rinse water and TOC data will provide more complete information from which to assess the efficacy of cleaning operations on an every run basis, yielding comprehensive and ongoing control well beyond the current status quo.

The monitoring and control of critical quality attributes for cleaning operations offer further economic and quality benefits in reduction or elimination of cleaning related OOSs and their associated investigations and resolutions. These cost reductions can be realized not only through more efficient processes that facilitate faster and more flexible production schedules, but also through the minimization of labor hours invested in manual operations required to support systems, through manual sampling and analysis, which cannot provide the same sensor based process control information. In many manufacturing facilities, cleaning validation samples are manually collected and submitted for analysis to Quality Control laboratories, or in some cases to off-site contract analytical laboratories. These activities involve both time and expense for the manufacturer in the form of labor hours for collection of the data, sample collection materials, time and resources of the QC laboratories, and opportunity cost related to delays in manufacturing operations from waiting for analytical results to determine if cleaning processes were successful.

Finally, the economic benefits of online sampling are supported by the time recorded in the execution of this study to conduct the manual sampling and analysis as compared to the time investment required for running the online analyzer during CIP operations. The time required for the collection preparation and analysis of the samples collected for nine cleaning runs was in excess of 80 labor hours. In contrast, the total set up time for the online analyzer was approximately three labor hours. On a per-run basis, preparations for online analysis and sampling required approximately 20 minutes. In comparison, each run required nearly 10 hours of labor for manual sample collection and analysis. Clearly, extrapolating this time savings over the period of a year indicates that

significant savings may be realized, the magnitude of which depends on the particular facility and the number of cleaning operations to be qualified and monitored. Although integrating online TOC measurements into CIP system automation will result in added capital costs, operating costs can be significantly reduced and will likely justify the investment.

Summary

Sophisticated measurement and control strategies have been successfully applied to CIP systems and operations for many years. The utilization of online TOC measurement represents a significant step forward in assurance of product quality and safety through more effective real-time monitoring and control of the cleaning processes. With enhanced quality assurance and reduced cost of goods as driving forces, pharmaceutical manufacturers are automating manufacturing operations to accommodate more complex processes, including more complicated cleaning sequences commensurate with increasingly complex manufacturing equipment configurations and production methodologies. More robust automated systems will provide higher levels of assurance of removal of potential contaminants to acceptable levels. CIP systems can be automated to the point that risk from manual operator actions are eliminated from the process stream, except for manual set-up activities, such as the loading and un-loading of a glass-washer or the starting of a unit operation from a control point.

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Acknowledgements

The authors gratefully extend their thanks to ASEPCO for their sponsorship of this project and allowing us to share the collected data and to GE Analytical Instruments for the generous loan of online and laboratory TOC analyzers.

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