GE Water & Process Technologies
Analytical Instruments

Case Study

At-line TOC Reduces Cleaning Verification and Product Changeover Costs By 92% For Pharmaceutical Manufacturer

Challenge

A leading BioPharma manufacturer of life-sustaining proteins that minimize the effects of chemotherapy faced cleaning validation challenges. This company's mature, validated production facility used state-of-the-art technology to ensure its processes ran smoothly, safely, and cost-effectively. For example, instead of using a very specific HPLC method to analyze routine swab samples for cleaning verification and product changeover, the company already recognized considerable savings by using a non-specific, total organic carbon (TOC) analytical method.

They were also in the process of validating TOC for a worst-case challenge compound at four areas on a protein purification column used in their process stream. Their four-week pilot validation study revealed that their laboratory-based protocol for cleaning verification (routine verification and product changeovers) would add an estimated $54,000 to their cleaning verification costs. If the company continued to operate in this current state, their cleaning verification costs would exceed $500,000.

Although not a trivial process, significant non-productive, labor-intensive time goes into running aqueous cleaning samples in a laboratory. However, cleaning verification costs go well beyond a lab technician journeying to the manufacturing floor, pulling a sample, and taking it back to the lab. Assuming a test instrument is available, the employee loads the sample and waits for the processing to end. After getting the results, the employee spends even more time entering the results into lab and equipment notebooks, and completing the reports. The left side of **Figure 1** shows this current process map.

The company calculated that during a typical four-week period it would take 895 hours to test the 371 samples generated from these four sites on the purification column—samples required for cleaning verification and product changeover. The cost for these samples was estimated at $53,700. In addition, it could take up to 48 hours to get the results back from the lab and resume production—a large part of the production schedule. They decided against laboratory analysis and looked for a less costly approach.

Solution

The facility evaluated various alternatives and decided to use at-line TOC. Similar to on-line sampling, an at-line sample is taken close to (but not within) the process stream and analyzed on the spot using a portable analyzer. The right side of **Figure 1** shows that this methodology virtually eliminates the non value-added, costly steps of the TOC sampling process. The results are ready in just 30 minutes, and the employee simply records them on the production record.

The company selected the Sievers 900 Portable TOC Analyzer, manufactured by GE Analytical Instruments, because it addressed their three main concerns. First, the TOC methodology (Sievers UV persulfate, membrane-conductometric) was already validated in their lab, so they were comfortable with the technology. They were also encouraged that the documentation and reporting requirements would be far less labor intensive because the FDA supports at-line methods.[1] The manufacturing team could pull the sample, run it on the analyzer, and quickly document the results. They would not need to wait for Quality Control (QC) to post the results and approve the equipment. The at-line TOC method moves the sampling procedure out of the lab and onto the production floor.

The second challenge was proving that the 900 Portable analysis results were equivalent or better than their laboratory results. In the lab, they verified results by

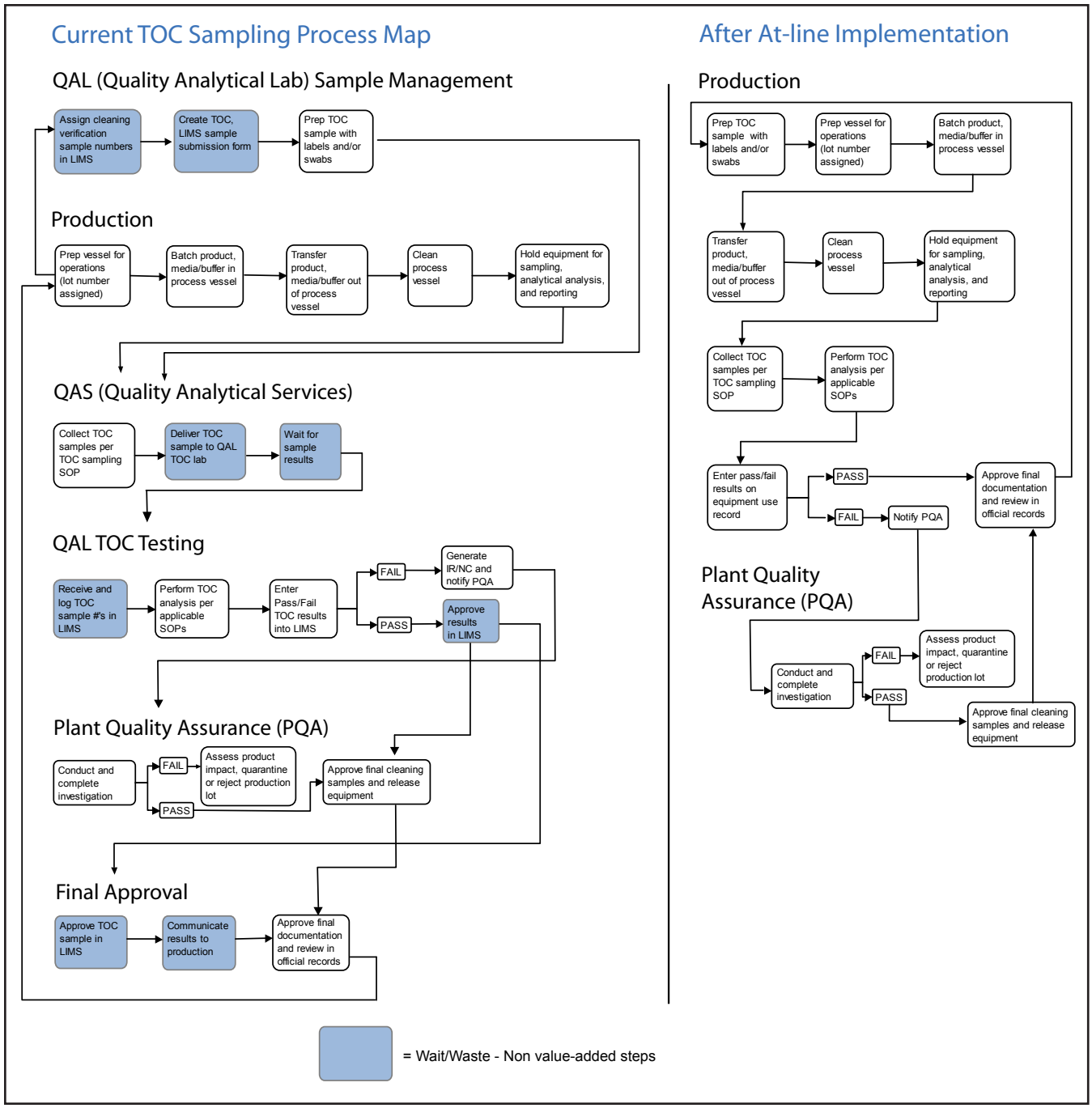

Figure 1. Sampling process map

conducting a standardization or a system suitability test prior to running cleaning validation samples. Fortunately, the procedure was the same using the 900 Portable Analyzer at-line, and test results demonstrated that the TOC methods were "equivalent."

Their third challenge was transferring knowledge about the instrument and method to the production staff. This proved not to be an issue, however, since the employees on the production floor only needed one 60-minute training/qualification session to become comfortable with the instrument.

Results

After completing the necessary change control evaluation and documentation, this company recognized considerable cost savings immediately upon qualifying the 900 Portable Analyzer. Because the instrument is portable, the manufacturing team was able to conduct sample analysis in multiple production suites. The total cost for the analyzer; a year's supply of vials, swabs, and standards; and the equipment validation was only about $40,000—much less than the estimated $500,000 for laboratory testing.

The company compared the costs of their lab-based TOC method to the cost data they had gathered thus far with the at-line TOC analyzer. They estimated that moving TOC out of the lab and onto the production floor will decrease annual sampling costs for cleaning verification and product changeover by as much as 92% (**Figure 2**). In addition, QC and manufacturing groups were using their time more efficiently. Processes no longer suffered interminable delays; instead, employees were able to document analytical results in real time and sign off validation packages and product changeover records quickly with a high level of confidence (**Figure 3**).

Part of the company's strategic plan was to move their production process toward the FDA's Process Analytical Technology (PAT) initiative.[1] PAT is a framework for manufacturing quality into the final product. Although process changes in the pharmaceutical world are difficult to control and document, the company recognized that change is part of good practice—part of being current and innovative. The FDA agrees, and its PAT initiative encourages the pharmaceutical industry to develop and implement new technologies such as at-line TOC.

Instead of undergoing a costly, time-consuming move to the at-line method, the company successfully and easily validated the change in its cleaning verification protocol. They effectively demonstrated that at-line TOC methods are a low-cost way to implement the PAT framework.

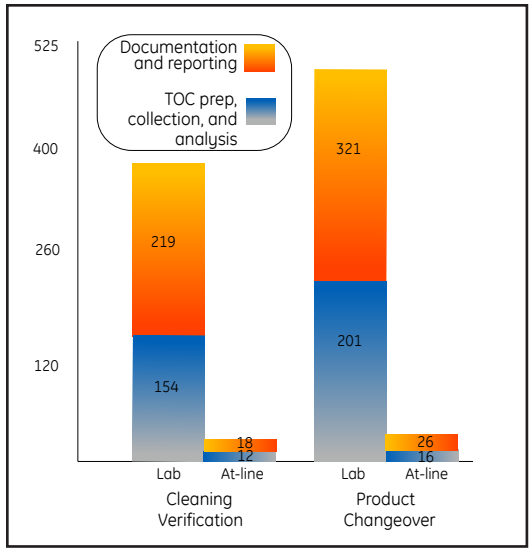

Figure 2. At-line TOC reduces cost by 92%

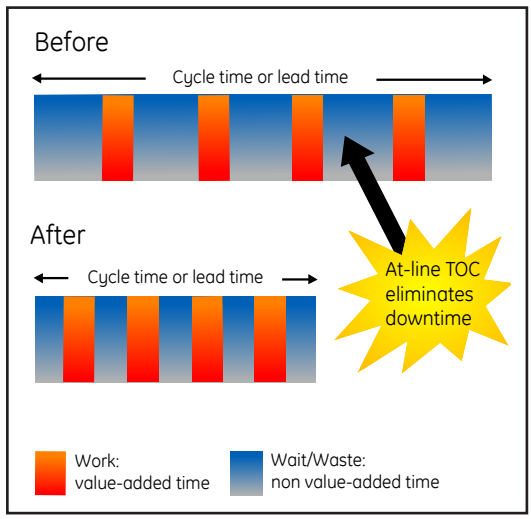

Figure 3. At-line TOC reduces cycle time

[1] Federal Drug Administration, "Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." 2004. http://www.fda.gov/cder/guidance/6419fnl.pdf

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