

Keeping PAT Projects Simple: Wyeth and GE Analytical Instruments Team Up to Demonstrate that Even Relatively Simple PAT Projects Can Deliver Big Benefits

Background/Challenges

Controlling costs and maximizing productivity of manufacturing assets are a priority for every pharmaceutical manufacturer. However, during growth stages, pharmaceutical companies are often forced to focus on expanding capacity — even at the expense of cost control and efficiency — in an effort to meet patient demands for products before competitors and/or generics provide an alternative source. The added demands of stringent product quality requirements and regulatory compliance present additional business challenges and often strain existing resources.

These challenges are not new of course, but in recent years the FDA and the pharmaceutical industry have been focused on promoting a more science- and risk-based approach to manufacturing drugs that can alleviate many of these manufacturing challenges. By analyzing and controlling — in real-time or near real-time — the critical quality attributes and variables in a validated manufacturing process, the process itself is what assures compliance with product quality requirements. Thus, the burden of inefficient and labor-intensive off-line, post-production quality control is greatly reduced. Focus shifts from product performance relative to regulatory limits and product specifications to process knowledge and capability. This knowledge can be leveraged into gains in manufacturing efficiencies, cost reduction and continuous process or product improvement.

Process Analytical Technology (PAT) is the term applied to this concept or system. But PAT encompasses a wide range of issues, and consequently, the concept of PAT is often viewed as being nebulous, even if its benefits



Sievers 500 RL On-line TOC Analyzer

are well understood. Ask ten people to define the benefits of PAT, and you'll likely get ten very similar answers; ask those same ten people to define what PAT is, and you'll likely get ten very *different* answers. "PAT Projects" are underway at a large number of pharmaceutical companies, often manned by PAT teams comprising large, cross-functional memberships. While there is undoubtedly value in the work that is being done on a large scale, Wyeth and GE Analytical Instruments tried a different approach — think big, but keep it simple.

Wyeth set out to address a manufacturing capacity challenge, and found that PAT provided the framework for a solution that was far less complex than the problem it solved. Though it may lack the glamour of broad-reaching PAT projects, this is the essence of PAT



— intelligent, innovative and science-based changes that simplify the complex while ensuring and even improving quality. Just because PAT has relevance for every aspect of pharmaceutical manufacturing doesn't mean that a PAT project need be all-encompassing. Viewed from the other direction, a PAT project of relatively limited scope can still yield significant gains in quality, efficiency and compliance.

Opportunities

Before starting the TOC PAT project, a well-defined risk assessment was performed on the water systems and the TOC sample plans. A Wyeth PAT engineer identified two key areas for improvement from the assessment:

1. Reduce TOC sampling and analysis costs
2. Eliminate production delays associated with TOC sampling inefficiencies and Out-of-Specification (OOS) results.

The challenge, however, for both opportunities was finding a way to automate the TOC sampling process and report results for the water in real-time without making significant changes to systems that could affect production or product quality.

Wyeth operates on a 24/7 manufacturing schedule and requires most quality control/assurance resources to support production activities, which include quality checks and production record review. With limited resources available to sample and analyze 25 water points of use on a daily basis, Wyeth needed to reduce the amount of samples and the inefficiencies associated with the current manual sampling method. Wyeth also wanted to reduce the cost associated with the laboratory TOC and conductivity sampling, calculated by Wyeth to be over \$82,000 in monthly costs, or approximately \$985,000 annually.

Not only was the current TOC sampling process costly, but the sample frequency and OOS results were contributing to various production delays. Due to the limited resources available to conduct TOC sampling and perform laboratory analyses, there were often significant delays in processing the samples and communicating the critical TOC "passing" results to the production floor. This left only two options: production delays due to waiting for results, or "running-at-risk" until the water was "approved for use."

Running at risk was occasionally the only option, given a tight, non-flexible production schedule. In the case of OOS TOC results, the outcome would have a greater impact on the production schedule. When an OOS occurred, the QC department had to shift limited resources to investigate whether the failing TOC was attributable to a water system upset or a sampling error introduced during sample collection. Without "alert" or "action" controls in place — made possible by continuous, on-line monitoring — Wyeth was only able to respond after an OOS result was generated, further compounding the delays associated with manual sampling and analysis. In the event of actual water system upsets, on-line monitoring would have alerted operators to abnormal trends, facilitating a real-time response to avoid reaching action levels.

Wyeth sought to transition from a fixed, manual and costly process that was susceptible to sampling errors and production delays to a process of continuous monitoring that would provide real-time performance data, alert and action levels, and that would eliminate the variability introduced by manual sampling while also liberating valuable human and laboratory resources.

Solution

To address these production and quality control challenges, the Wyeth plant installed four Sievers 500 RL On-Line TOC Analyzers from GE Analytical Instruments on their PW and WFI systems, capturing all points of use. Wyeth also implemented a monthly periodic monitoring point-of-use sampling program for added compliance and assurance. Even though the on-line data is sufficient to demonstrate that the water system is not trending out of spec over time, Wyeth considered this grab sampling as a best practice approach to ensure there were no variables that would contribute to a potential water system failure.

"We selected the 500 RL Analyzers from GE Analytical Instruments because of the ease of use, superior analytical performance, and the peace of mind that the analyzers would be in line with FDA regulations and [PAT] initiatives. The analyzers also allowed us to validate the method quickly and efficiently with GE's on-site validation services," affirmed the Wyeth PAT Engineer, who is responsible for the PAT project.



The 500 RL On-Line Analyzers are operating continually to monitor and release the PW and WFI waters feeding the production processes and are reporting TOC and conductivity results to a validated SCADA control system. Alert and action alarms are set up via the SCADA system, at 250 ppb and 350 ppb respectively, to alert operators to unusual water system TOC trends. The alert and action alarms are set up so that the water system never exceeds the 500 ppb TOC regulatory limit unless there is a gross contamination or failure. If the water system exceeds the 500 ppb limit an OOS alarm is triggered. At this point QA and operations individuals are notified electronically and the automation is validated to lock down the system so water is not released for further production uses.

Additional benefits for selecting the 500 RL for this project included the optional Super iOS (Integrated On-Line Sampler), which provides advanced automation capabilities. The Super iOS fully automates system protocols such as system suitability, calibration, verification and linearity via cartridges that house all the standards needed for any given protocol; the analyzer automatically sequences through the vials and will even restart TOC analysis upon successful completion of the protocol.

The Super iOS also provides advanced data management capabilities — eliminating the need for manual transcription and record keeping — and 21 CFR part 11 security features. Information or metadata about the standards lot number, compounds, concentrations and expiration dates are programmed into a memory chip embedded in the vial set cartridge. The analyzer's software reads this data once the standards cartridge is inserted into the Super iOS and incorporates the information into electronic documentation, eliminating the potential for manual transcription or documentation errors. The results of the protocols and the standards' metadata can be exported in an encrypted format to a USB device or through a serial computer connection. The encrypted file is then opened in the associated DataShare software which allows for viewing and sharing of data while precluding modification, thus facilitating 21 CFR part 11 compliance.

"The 500 RL's Super iOS allows me to simultaneously perform all my system suitability testing on every analyzer

at one time. What is great about the Super iOS and the standards cartridge is that all the data is 21 CFR part 11 compliant, automated and, once the test is complete with passing results, the analyzer automatically restarts its analysis."

The Wyeth PAT Engineer also added, "While it used to take me eight hours to perform the testing on our previous instrumentation, it now literally only takes me minutes. I open the standards package, insert the cartridge into the Super iOS and press start on the touch screen to run the specific protocol (e.g. system suitability, calibration, verification). The only time I have to return to the analyzer is to remove the standards cartridge, export the data and print out the reports for Wyeth's production records." These enhancements also contributed to Wyeth's efficiency gains in productivity and resource utilization.

Results

By aligning PAT quality strategies and innovative TOC technologies, Wyeth was not only able to increase resource utilization, they also were able to drive improvement in quality practices. As a result of the 500 RL Analyzer's on-line analysis, the Wyeth facility reduced manual TOC sampling by 97%, simultaneously reducing the variability associated with manual grab sampling that had been demonstrated by numerous OOS TOC results. These sampling reductions in turn reduced the relative sampling costs by \$915,000 per year after capital costs, installation and validation of the analyzers. The plant has also reduced OOS investigations by 65% and decreased its lot release times by 40%, resulting in better quality, increased production efficiency and decreased costs across all facets of the manufacturing process.

"The on-line TOC project has exceeded our expectations for operational efficiency, financial gains, and quality benefits," said the Wyeth engineer. "This implementation will enable us to be proactive with our quality programs and future change control projects. In financial terms, the analyzers were easily justified, showing excellent return on our investment. Although the gains in efficiency are nice, the true benefit is having better control of our sampling process and quality of our water systems."



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