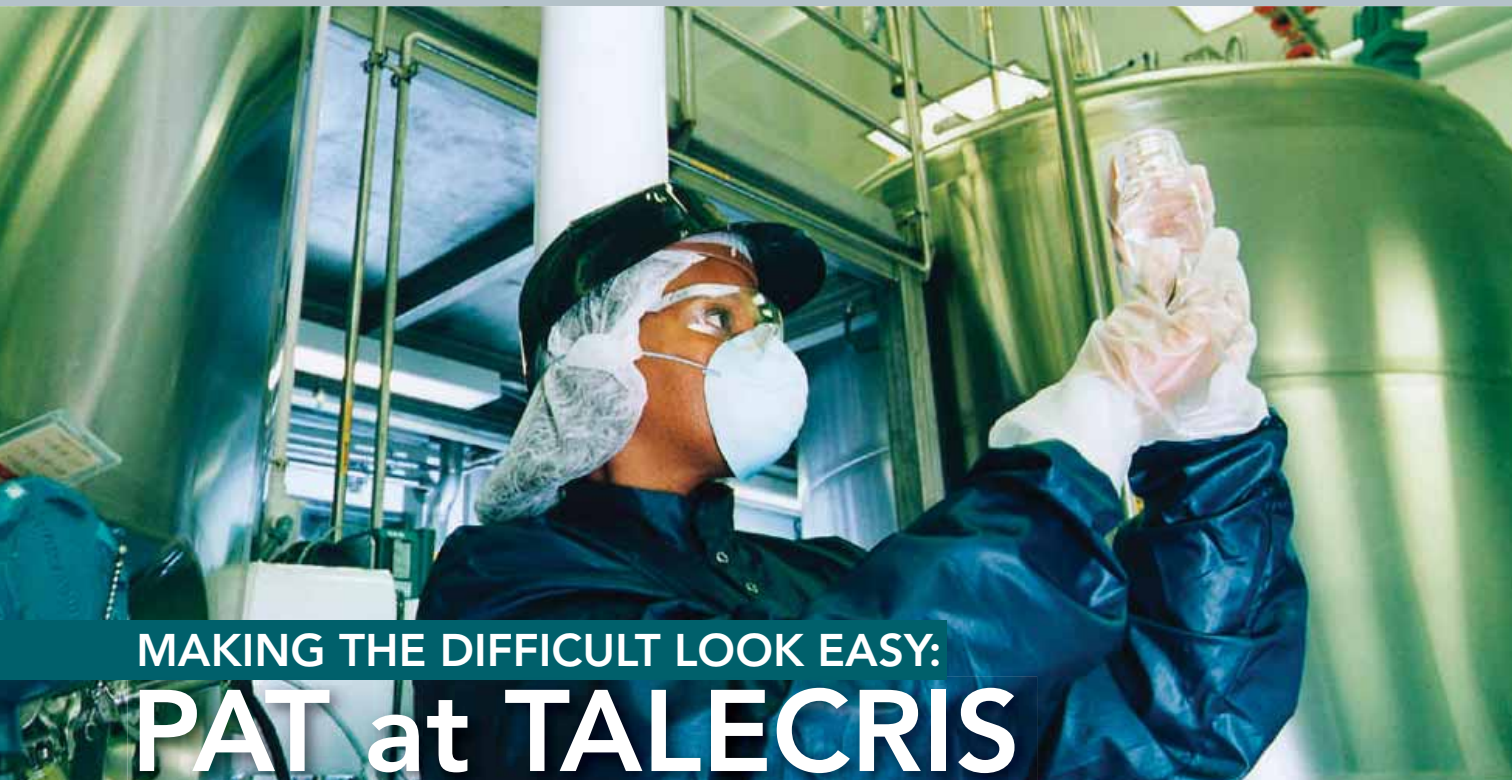


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MAKING THE DIFFICULT LOOK EASY:

PAT at TALECRIS

MULTIDISCIPLINARY FORETHOUGHT HAS BEEN THE KEY TO MAKING PROCESS ANALYTICAL TECHNOLOGY WORK FOR FRAGILE PROTEIN THERAPIES

By Gerrit Vogel, Joydeep Ganguly, Dr. Anne Bertelsmann, Dr. Douglas Burns, Dr. Gerold Mohn, Dr. Prasanna Deshpande, and Dr. Pete Vandeberg, Talecris Biotherapeutics*

At a time when controversy still surrounds the application of process analytical technologies and advanced control to biopharmaceutical manufacturing, the therapeutic protein manufacturer Talecris Biotherapeutics is making great strides in improving the analysis and control of its processes. In this article, Talecris' PAT team summarizes best practices and recent examples of success.

Fragile proteins are at the heart of some of the most important life-saving therapies available today. However, manufacturing these proteins can be far more challenging than making traditional pharmaceuticals. One of the greatest challenges is simplifying and controlling the manufacturing process, a process that is itself changing as micro-organisms

adapt to their environments.

Nearly 10 years ago, we sought a structured process for analysis technology, in order to better monitor and control the manufacture of our fragile protein therapies. Looking back, we now realize that we were striving toward the goals of process analytical technologies (PAT). Since then, our use of PAT has evolved to keep

up with new manufacturing processes and technologies, and most recently with FDA's PAT guidance [1], released in September 2004.

In order for PAT to truly be effective and useful during the entire manufacturing cycle, it must reflect all aspects of the manufacturing process and encompass all business segments that stand to benefit

Above: A Talecris technician analyzes a production sample for clarity.

* Talecris is based in Research Triangle Park, N.C., with facilities in Clayton and Raleigh, N.C., and Melville, N.Y. It was formed in 2005, when the assets of Bayer HealthCare's Biological Products Division's plasma business were purchased by private investors.



Brandon Fincher monitors critical solution conditions during an optimization experiment in the development laboratory. Continuing process development and optimization are required for improved product quality and increased availability of essential protein therapies.

from FDA's guidelines. It was important to establish an organizational framework to support PAT.

We began by forming a multi-disciplinary core team whose mission is to promote initiatives and review opportunities for PAT application. This team's direction is then executed by a PAT implementation and coordination group, which was formed to prepare proposed PAT solutions for evaluation and, once approved, to coordinate and facilitate the execution of a PAT effort.

The next step was to develop a "PAT Master Plan" to define our company's interpretation of the FDA guidelines. The master plan serves as a road map for all PAT implementations—from initiation to execution—and ensures consistency across all company efforts. Within the master plan, the core team outlined five implementation steps to achieve process understanding for any PAT effort:

1. Identify an opportunity that would benefit from a PAT approach. For each opportunity, this required also identifying the critical quality attributes that must be monitored and controlled during the process.
2. Monitor the process through the use

of on-line instruments.

3. Statistically analyze the process to determine how the critical quality attributes relate to the efficacy of the overall process. This includes the development, verification and validation of any statistical models that could define the process.
4. Ensure control of critical quality attributes at all times and within specified limits.
5. Report findings to ensure that the process is in control throughout the processing period.

How do these steps come together day to day? Typically, PAT projects originate from a particular business unit's "need," when someone from that unit contacts a member of the implementation team to formally request PAT support.

That implementation team member then develops a detailed scope, benefit and timeline and puts the potential project on the PAT project list, which the core team then evaluates, using the master plan to determine whether or not to pursue the project and how to rank its importance among other PAT initiatives. Once any project is approved, the implementation

team develops a business case for the project and presents it to management for funding. The implementation team then works with the project management organization to bring the project to fruition and monitor its results following implementation.

This multidisciplinary approach, and the full support of corporate management, have allowed Talecris to complete numerous successful PAT initiatives in relatively little time. Nearly 20 PAT projects are now in process at the company, which together promise to have extensive and broad-reaching benefits.

The following are three related examples that have already delivered encouraging results and benefits, and demonstrate the value of a multidisciplinary approach to PAT.

REPLACING MANUAL SPARK TESTING

Utilizing PAT principles, Talecris' packaging department was able to develop a way to monitor seal integrity in lyophilized products, moving from a manual, subjective testing method to a more robust system, resulting in faster, more accurate and more reliable readings.

Talecris, like many other biological manufacturers, uses lyophilization, or freeze-drying, to prolong the shelf life of proteins. Lyophilized products are sealed under vacuum at our manufacturing facility. The end user then reconstitutes the lyophilized product with a diluent supplied in separate vials. Transferring the diluent into the product depends upon the vacuum in the product vial. Thus, the vacuum is not only an indication of the integrity of the container's seal, but is also necessary for the end user to reconstitute the product.

Before our PAT implementation, Talecris' packaging department used spark testing to inspect lyophilized products, manually, for vacuum leaks. Although spark testing is one of the most common methods for in-process vacuum testing, it has its drawbacks: high voltage can damage delicate proteins, while false positives are common. Even when the test runs successfully, it fails to provide a quantitative measure of the vacuum in the vial.

Based on published literature [2], we evaluated a new online frequency modulation spectroscopy (FMS)-based technology to replace spark testing. Aside from its important benefit of not exposing the product to high voltage, the on-line technology allows for automated, real-time inspection of vials, eliminating all subjectivity from the manual inspection.

Unpublished studies at Talecris confirmed that approximately one-third of the vials rejected during spark testing were actually shown to be vacuum-sealed when tested using the nondestructive FMS-based analyzer. Finally, by providing a quantitative measurement of the pressure in the headspace of the vial, Talecris can assure a level of vacuum sufficient enough to transfer the necessary amount of diluent into the product, as the level of pressure varies for different product vial sizes and diluent amounts.

ACETONE DRYING: A BETTER PROCESS FOR ALBUMIN

Albumin is the most prevalent protein found in blood and is often used as a stabilizer in the manufacturing of several biologic therapies. During the manufacturing process, albumin paste is produced and rinsed with an acetone solution, an important viral inactivation step. The paste is then dispensed into stainless steel drying pots for a specified time in order to complete a lengthy drying process. At the end of the drying process, samples are taken from each drying pot and sent to the lab, where they are tested for acetone content. However, since moisture and acetone are not homogeneously distributed in the paste, the minimum time to reduce acetone levels below the limit may differ from run to run and even between different drying pots. This reinforces the need for accurate analysis, but also makes obtaining representative samples difficult.

In search of a more efficient method of testing and to better understand the albumin paste drying process, the PAT core team approved the use of a hand-held photoionization detector for the real-time monitoring of the acetone content, or dryness, of the paste while in the drying pots.


Since it began using the detector, the Talecris production crew has realized a number of benefits in addition to improved process control. The replacement of the laboratory test with the real-time test has not only reduced cycle time, but has also saved the organization approximately \$250,000 per year. Drying time for the paste has also been reduced by 30%, therefore increasing throughput in the drying process. Lastly—and most important to Talecris—on-

line monitoring reduces the risk of microbial contamination that is always possible with manual sampling.

INCREASING YIELD THROUGH ANALYSIS OF EXISTING DATA

Using a methodology rooted in a Six Sigma approach, scientists at Talecris implemented a significant improvement in the yield of the Alpha-1 Antitrypsin protein, a naturally occurring protein found in human plasma. By analyzing data, the PAT team discovered numerous ways to improve the yield of the protein, the most promising of which involved a reduction in the flow rate during a certain phase in the manufacturing process.

After analyzing published data [3], the team hypothesized that the existing flow rate was higher than optimal for protein recovery. Thus, it performed an assessment within the manufacturing process by tightly controlling the flow rate for a statistically significant number of batches. The team found an 8% increase in yield of the Alpha-1 protein.

While PAT at Talecris continues to evolve, the organization's most recent implementations have delivered very encouraging and valuable results. Within the organization, PAT has been deployed on various processes, utilities and packaging areas, resulting in yield improvements, cycle-time reductions, increased quality assurance and better process understanding. The multidisciplinary approach, supporting infrastructure and full management commitment provide Talecris with the foundation to be innovative and successful in its PAT efforts. 

About the Authors

Gerrit Vogel was an engineering manager

at Talecris Biotherapeutics, who chaired the company's PAT effort. An electrical engineer by training, Mr. Vogel's responsibilities included project and operation management of all control systems, electrical equipment and instrumentation on-site. He has more than 15 years of experience in plant and project engineering, coupled with eight years of experience in engineering management.

Joydeep Ganguly was the PAT group lead at Talecris. He holds an M.S. in Electrical Engineering from the University of Notre Dame and is currently pursuing an MBA from North Carolina State University. His areas of expertise include statistical process control, automation, data analysis methodologies for biological processes and analytical instrumentation.

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