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Modernizing Pharma Operations With Process Analytical Technology

- PAT for Performance Improvements
- DeltaV™ Spectral PAT
- Leveraging PAT in Modern Operations

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Integrated Process Analytical Technology (PAT): A Path to Improved Performance

By Molly Firkins, DeltaV Product Marketing Manager at Emerson

Embedding process analytical technology (PAT) within a control system simplifies a traditionally complex architecture and offers pharmaceutical manufacturers the means to increase their speed to market.

It's the same for manufacturers across industries and across the globe; there's a steadily increasing pressure to meet market demand, despite facing new challenges and constraints. Whether it's overcoming supply chain issues, adapting to worker shortages, or dealing with inefficient processes and aging equipment, in essence, it all comes down to that ages-old axiom of "doing more with less." And that means, regardless of industry, producers need to be getting more from their existing operations.

Today's pharmaceutical manufacturers, in particular, are faced with a number of challenges largely stemming from a burgeoning global population. Specifically, they're being asked to not only produce more treatments but also a wider

variety of treatments. These dual and equally important demands are the result of an ever-expanding patient base – a contingent characterized by an increasingly diverse set of needs and requiring more personalized medicine and customized dosing. What's more, pharmaceutical manufacturers are being asked to deliver these treatments to market faster than ever – all while ensuring the quality and safety of these products.

To characterize this landscape as "challenging," would be an understatement. Fortunately, advancements in digital technologies are providing incredible opportunities for pharmaceutical manufacturers to transform their processes in ways that create new efficiencies and propel operational performance to heretofore unseen levels. By leveraging these new technologies, manufacturers can, in effect, digitalize the drug development process and create a clear path to consistently hitting production goals and driving long-term profitability. The key, however, is identifying which of these technologies and approaches will actually move the needle.

To that end, one of the most promising new advancements for the industry is the integration of process analytical technology (PAT) into control systems. The embedding of PAT *within* a control system represents a paradigm shift in the approach to process analytics typically adopted by pharmaceutical manufacturers. And at a time when speed to market is critical, this new approach to PAT provides a path to significantly faster product release.

Process analytical technology, in and of itself, isn't new to pharmaceutical manufacturing; in fact, many operations have incorporated PAT to some extent in an effort to achieve more control over their processes through closed-loop process verification. The traditional approach to achieving this, however, has proven complex – and, at times, discouraging – because it requires time, resources, and targeted expertise. What's more, personnel are often left to manage fragile systems that need significant upkeep throughout their lifecycle.

WEBSITE

DeltaV Systems and Software for Life Sciences

Part of the issue arises from dealing with the vast amounts of raw data generated by spectral analyzers. These instruments are essential to PAT, collecting important, multivariate data about a batch – usually 3,000-4,000 spectral variables per scan. As you might imagine, making sense of this much data isn't easy. Data scientists must first use multivariate data analytics packages to develop and validate complex models that convert these spectral arrays to critical process or product attributes. These models then must run on servers that typically reside at Level 3 of the Purdue control hierarchy to translate real-time spectral data into useful information before passing it to the control system, at

which point it can be used by operators to adjust a process.

If moving large amounts of multivariate data from the lab to the plant floor sounds complex, that's because it is. Just consider the multiple, disparate systems required to make it happen: Analyzer instrument systems must first capture and make available multivariate data in real time to a PAT application that can apply the data to a model and generate results that must then be shared with the control system. This layered approach creates a complex architecture for information technology (IT) and operational technology (OT), from implementation throughout the system's lifecycle. It also inadvertently creates a system vulnerable to compatibility issues that could crop up and derail production if one component in this delicate chain is altered.

Simply put, integrated PAT offers a better way. Bringing spectral signals directly into the control system collapses that layered architecture, enabling raw spectral data to be analyzed, and control decisions executed — all in one simplified process. The result: a more stable, closed-loop and repeatable process that enables real-time monitoring of quality and increases speed to market.

It's all made possible with the right control system – in this instance, Emerson's DeltaV™ distributed control system. The DeltaV DCS is an easy-to-use, ISASecure-certified automation system for the process and hybrid industries that offers a full suite of advanced control applications aimed at improving plant performance. To fully leverage PAT, DeltaV makes use of well-known industry-leading chemometric model engines such as SIMCA®-Q from Sartorius or AspenTech's Aspen Unscrambler™, which are embedded into a standard function block running on the system's application station.

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These model engines are complex tools but suffice it to say they are critical for translating data into actionable information. Aspen Unscrambler, for example, is a multivariate data analysis solution that has continued to evolve to meet the needs of the industries it serves, building upon a proven, decades-long history of helping manufacturers optimize their operations. Through numerous collaborations with analyzer providers, convenient workflows have been developed for model build, model validation and model maintenance for a wide range of spectroscopic PAT instruments. Furthermore, persistent attention to changing regulatory compliance

requirements of the industry has resulted in features that support compliant and secure multivariate analysis workflows.

By embedding models from Aspen Unscrambler or SIMCA-Q within the control system, the system can directly receive spectral data and perform chemometric model calculations on that data in real time, generating critical quality attributes about a product. And because DeltaV Spectral PAT leverages the DeltaV configuration, database and support infrastructure used by other control applications, complexity is reduced, process validation is simplified, and overall system security is enhanced.

But simply having the information is only half the battle; ensuring actionable information gets to the right people is paramount. That's why DeltaV features a modern, intuitive operator interface designed to deliver continuous insights to operators so they stay informed and can take action. Online measurements and quality calculations are easily accessible, and operators can be instantly alerted to deviations, allowing them to make adjustments that save batches. This means products stay on spec and get to market faster.

Integrated PAT systems also can establish a foundation for more effective regulatory management, helping ensure product safety and simplifying the audit process. For example, these systems have built-in solutions to show and document safe, accurate, repeatable processes. In addition, change control mechanisms help confirm processes are using the right model versions, and real-time diagnostics can confirm analyzers are working properly.

In today's manufacturing landscape speed to market is everything. Pharmaceutical manufacturers no longer have the luxury of allowing a product to sit in work-in-progress. They must be flexible, fastidious and fast, and the integration of spectral waveform data directly into the control system represents a significant opportunity to increase speed to market by automating product release and optimizing throughput – quickly, effectively and safely.

Molly Firkins

DeltaV Product Marketing Manager

Emerson

ABOUT EMERSON

Emerson (NYSE: EMR), headquartered in St. Louis, Missouri (USA), is a global technology and software company providing innovative solutions for customers in industrial, commercial and residential markets. A leader in industrial automation, Emerson helps process, hybrid and discrete manufacturers optimize operations, protect personnel, reduce emissions and achieve their sustainability goals through its Automation Solutions and AspenTech businesses. Emerson's Commercial & Residential Solutions business helps ensure human comfort and health, protect food quality and safety, advance energy efficiency and create sustainable infrastructure. For more information, visit Emerson.com.

Implementing Real-Time, Closed-Loop Process Control Using Spectral PAT

Q&A with Bruce Greenwald and Molly Firkins

Bruce Greenwald
Business Development Manager,
DeltaV Distributed Control Systems,
Emerson

Molly Firkins
Product Marketing Manager,
DeltaV Batch,
Emerson

Embedding DeltaV Spectral PAT directly into the control system enables life sciences manufacturers to take a simplified approach to achieving real-time manufacturing, compliance with confidence, greater return on investment (ROI), and delivery of quality treatments to market faster.

PharmTech: What factors are influencing the current landscape for life sciences manufacturers?

Greenwald: It's more important than ever for our pharmaceutical manufacturers to deliver their therapies quickly and cost effectively around the globe. With the focus on rapid results, products can't sit in inventory for days or weeks waiting on lab testing or quality validation. Additionally, plants are putting a massive effort into digitally transforming their manufacturing process.

One of the goals that the FDA first released with their PAT (process analytical technology) guidance was for manufacturers to better understand the science behind their process. By better understanding the science of the process, they'd be able to fast-track the approval of those new therapies. The carrot, if you will, has now become mainstream today; people have to do this. The old way simply isn't going to cut it. Technologies have caught up and manufacturers are doing this, but it doesn't mean it's always been easy.

PharmTech: What challenges are life sciences manufacturers facing as a result?
Greenwald: The challenges really come down to the execution of obtaining the real-time quality parameter data for manufacturers to be able to release product or know if they have a problem. Process Analytical Technology, PAT, which relies heavily on incorporating multivariate spectral analysis data, is an important part of that process because of the tremendous pressure life sciences manufacturers are under to deliver treatments to market quickly and efficiently.

The traditional approach to PAT implementation has become antiquated. A fully manual approach to sample gathering and testing involves a lot of time-consuming steps and introduces the risk of human error. Quality tests are often performed after manufacturing is complete, delaying release and making it nearly impossible to recover from deviations. The financial impact, the losses, can be significant. Even with the help of recent technologies like inline spectral analyzers, that process has introduced a slew of new challenges.

PharmTech: With those inline analyzers that work to automate the PAT process, you mentioned the introduction of new challenges for life sciences manufacturers. Can you expand on those?
Greenwald: With all good intentions, these inline analyzers have created multiple execution layers, user interfaces, disparate systems, and potentially fragile architectures. This is the slew of challenges I mentioned that ultimately make implementing, maintaining, and validating this PAT approach difficult. Still, the need to ensure treatments are thoroughly tested, using complex multi-variable data, remains a requirement.

VIDEO

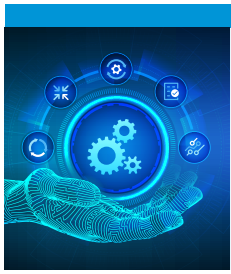
Improve Speed to Market with Real-Time, Closed-Loop Control

PharmTech: What solutions are being brought to market by Emerson to help life sciences manufacturers overcome these challenges?
Firkins: At Emerson, we have the DeltaV distributed control system, which allows enhanced decision integrity with greater insight. It also provides embedded security with real-time delivery and transfer of data to run your process.

Recently, we've introduced DeltaV Spectral process analytical functionality, our DeltaV Spectral PAT. Now DeltaV Spectral PAT was designed to help manufacturers meet the FDA guidance around PAT, where the ultimate goal was to better understand the science behind the process.

PharmTech: Can you talk a bit more about the DeltaV Spectral PAT, how it works, and how that translates into value for your customers?

Firkins: Emerson's Spectral DeltaV Spectral PAT collapses that complex fragile architecture of the traditional PAT approach. It's become possible because DeltaV Spectral PAT runs industry-leading chemometric models directly in the control system blocks. We use the OPC UA standard interface to communicate with spectral analyzers. Then a PAT model function block reads spectral array signals and performs the quality attribute calculations for real-time monitoring. Now, because we're deploying PAT directly in the control system, DeltaV Spectral PAT provides online measurements and quality calculations that provide continuous data for tighter control and less manufacturing variability all while minimizing human error.



PODCAST

Achieve Real-time, Closed-Loop Control in PAT Manufacturing

DeltaV Spectral PAT is easier and more cost effective to implement and maintain, because the users can leverage the standard DeltaV configuration, the database, and all the support infrastructure that are used by the other control applications.

Unlike the traditional solutions that Bruce mentioned with multiple layers and servers and communication dependencies, DeltaV Spectral PAT increases reliability with a robust architecture that's designed for uninterrupted communications and closed-loop control. DeltaV Spectral PAT is easier and more cost effective to implement and maintain, because the users can leverage the standard DeltaV configuration, the database, and all the support infrastructure that are used by the other control applications. Process validation is also simplified because applications are all part of the integrated DeltaV platform.

PharmTech: How does taking this new approach of implementing embedded DeltaV Spectral PAT help life sciences manufacturers not only drive towards fully automating their manufacturing process, but optimizing their process as well?

Firkins: There are a couple of takeaways here. When manufacturers work in a single integrated, intuitive environment, that's easy to implement and maintain. They can monitor multivariate data from the same

interface that they use to perform all their other control steps.

The system is also higher performing and it's more secure and easier to validate. Now the entire PAT solution is another component of the automation platform. Secondly, it's one thing to understand your process and to know if it's good or if it's bad, but with embedded DeltaV Spectral PAT, manufacturers have real-time access to data for the CQAs (critical quality attributes).

Not only is it easier to report them, it's easier to take that quality, real-time data and put it into action to make adjustments. It can make those adjustments when and where they need to in order to optimize their manufacturing process and keep their CQA in line. From that, we can also use model predictive control to go beyond the quality monitoring. We are now going to closed-loop control.

PharmTech: What's the bottom line?

Firkins: Ultimately, by using DeltaV Spectral PAT, our customers can help deliver quality critical treatments to market faster by moving plants toward fully automated production. Spectral PAT offers a simplified approach to their operations, where they can realize real-time manufacturing, set a foundation for greater regulatory compliance, and realize a faster return on investment to their stakeholders.

Effectively Leveraging Process Analytical Technologies in Modern Pharma Operations

Charles E. Miller
Director of Solution Consulting,
Aspen Technology

AspenTech and Emerson are leading the way in helping manufacturers fully integrate PAT into modern automation systems.

The integration of process analytical technologies (PAT) into modern automation systems represents a paradigm shift for pharmaceutical manufacturers looking to establish a better-performing PAT architecture that benefits their operations. We caught up with Charles E. Miller, director of solution consulting at Aspen Technology, to help us better understand the role of PAT in the industry.

Q1. Pharmaceutical manufacturers understand the value of optimizing their operations, and many are wanting to go about this by incorporating more inline monitoring capabilities with their systems.

What do they need to consider as they look to get started?

Well, process analytical technologies (PAT) that enable inline monitoring have come a long way in the past few decades, but they are not 100% cost- or risk-free, and therefore a compelling business case must be built. In the pharma industry, establishing such a case involves a formal risk assessment (RA) of the relevant process operation, where a diverse group of process stakeholders, including end users, management, engineers, and other subject matter experts carefully consider as many possible process failure modes as possible, based on existing understanding of the process. The typical output of an RA is a Failure Mode and Effects Analysis (FMEA), which lists and ranks these failure modes based on their frequency, severity, and detectability.

In many cases, the RA identifies risks that can be mitigated using inline monitoring technologies: for example, risk of a product quality (CQA) failure or risk of a process performance (CPP) deviation. In the pharma industry, both product quality risks and business risks are taken very seriously, and the nice thing about PAT is that it can address both types of risks. If it's determined that advanced analyzers are needed to mitigate these risks, these manufacturers will then need to scope and qualify the available measurement technologies and supporting automation technologies, and work with those vendors to create a strategic plan of action as they determine the technology and automation partner whose solutions will best meet their needs. They may consider questions such as: Is this technology easy to integrate with my existing process? Is it easy to deploy and maintain? And does it give us the data we need in the way we need it? Constraints also need to be considered when scoping technologies, such as limitations of on-site expertise and resources.

Q2. Traditionally, how would manufacturers have developed a workable solution and leveraged their data?

The integration and processing of analyzer data has a long and interesting history, reflecting the unique challenges of handling multivariate responses while accommodating instrument systems that are often complex.

In the early days of process analyzers, when state-of-the art PCs used 80386 processor technology, the processing of multivariate analyzer data was strictly in the realm of the instrument system, with calculated process or product attributes shared either manually, via analog (4-20 mA) signal, or via an early digital protocol (ex., Modbus) directly to a distributed control system. For the manual case, you can likely imagine all the inefficiencies and risks, and even the earliest analog and digital approaches had their challenges. This just wasn't (and never could be) a scalable or sustainable approach, especially as the global demand for PAT continued to increase. Moving ahead several years, analyzer vendors recognized the necessity of multivariate analysis (MVA) model build and deployment workflows around their instruments, and they improved

their bespoke analyzer management software to include these functionalities. Although these improved solutions did allow end users to develop and deploy MVA models on these analyzers, they were each typically limited to a single instrument make and model, and in many cases had very limited model build, model optimization and management capabilities. As a result, these were not particularly scalable or sustainable solutions, especially for end users who wanted the flexibility to use multiple analyzer technologies and suppliers.

One key advantage of our extensive third-party collaborations is the presence of solutions that use our "low-footprint" MVA prediction engine that executes MVA models at the point of measurement.

In more recent years, several suppliers stepped up to provide more wholistic PAT management systems (PMSs) that can accommodate different makes and models of instruments, thus providing a centralized location for all PAT functions. Most deployment architectures of these PMS solutions placed their key components at the DMZ level or higher, as most of the management workflows resemble more off-line "IT" type tasks. These solutions have gained a lot of traction in the pharma industry in recent years, but their extensive use has revealed some cases where this architecture is not optimal: for example, where network latency issues can affect timely delivery of results to the DCS, or where site security policies limit IT/OT communications. Furthermore, integration and validation of these systems can be quite challenging, as their communications span several levels of the architecture.

Q3. How does AspenTech help its clients with all the above?

AspenTech brings several key elements to address the above challenges: a legacy of successfully embedding "industrial artificial intelligence" into our clients' operations; a strong pedigree of MVA expertise; highly evolved data handling and MVA modeling tools; constant attention to the ever-evolving cGMP regulatory expectations for PAT in pharma; and a long history of collaboration with third-party providers of process analyzers and automation solutions. One key advantage of our extensive third-party collaborations is the presence of solutions that use our "low-footprint" MVA prediction engine that executes MVA models at the point of measurement- whether on the edge, in the field, or at the shop floor level. Such solutions avoid the pitfalls associated with model execution at higher architecture levels, discussed earlier.

Q4. How does Aspen Unscrambler work with Emerson's DeltaV DCS?

Analyzers, by themselves, produce spectral intensities, which are not necessarily useful

for process monitoring or control. AspenTech Unscrambler is the offline tool that is used to create the model that converts spectral intensities to process KPIs, which in turn gets embedded into DeltaV for real-time execution. DeltaV has the function block that can execute these models at a lower level in the architecture, which improves system performance and reliability, and simplifies system validation.

Just as DeltaV has well-integrated GxP compliance features, Unscrambler also has GxP compliance-readiness features supporting MVA model build, change management and validation, as well as audit trail and security. Furthermore, as an instrument-agnostic solution, Unscrambler can be used for model build workflows involving a wide range of analyzer makes and models, allowing end users to select the analyzer technology that is best suited for their specific needs.

Q5. So what does this all mean for pharma manufacturers in terms of impact to their operations?

On the deployment side, it provides access to a simpler, more resilient, more reliable, more secure, and better-performing PAT architecture that enables faster, smarter decisions about your production. On the development side, you have the benefit of a well-tested, optimized, and compliant solution for PAT model build and management workflows, which works well regardless of the analyzer technology that is chosen.

It's also very possible that this specific solution reduces the total cost of ownership of advanced PAT systems, in that the simpler architecture is more robust, easier to validate, and easier to maintain. Simply put, implementation of the system is easy. Maintaining the system is easy. And operations are one step closer to fully automating their manufacturing.

Charles E. (Chuck) Miller is director of solution consulting at Aspen Technology. He has more than 30 years of experience in applying process analytics and multivariate analysis to research and manufacturing problems in several industries, including chemicals, foods, materials, medical diagnostics and pharmaceuticals.