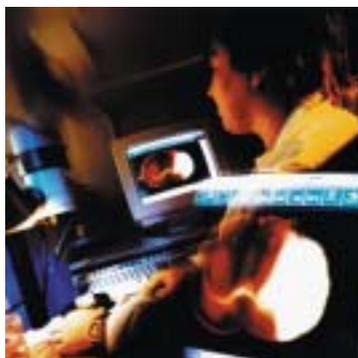


Filling the Void PAT in a Connected Manufacturing Environment

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The author brings attention to the connectivity problems among various data-gathering systems and discusses the drivers and benefits of change, including PAT.

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In his December 2002 editorial entitled “We’re All in This Together,” John Haystead, editor-in-chief of *Pharmaceutical Technology*, wrote about the single most important lesson learned by members of the pharmaceutical industry: “Information is worthless if it isn’t communicated.” He suggested that by having more-efficient information sharing capabilities, members of the pharmaceutical community will have to “enthusiastically endorse the principle that comprehensive, rapid, and efficient information sharing is not only beneficial but mandatory.” He couldn’t be more right.

The de facto standard in manufacturing processes is information systems that have been created separately, thereby causing data to be stored in silos. Working with data from the manufacturing process is often an ad hoc and time-consuming procedure through which pharmaceutical companies must report on operations and meet regulatory requirements. The result is a highly inefficient operating process. Compartmentalization is costing pharmaceutical manufacturers compliance and efficiency, and the situation will get much worse unless we take a new approach to getting the value out of our data-gathering systems.

The most recent driver for this change is process analytical technology (PAT). PAT processes are gaining mind share among pharmaceutical manufacturing executives as a way to improve operating efficiencies. PAT provides in-process measurements of quality in real time. PAT also makes large amounts of additional data available that can enable decision makers to make significant operational improvements, thereby increasing efficiency through improvements in cycle times, sta-

bilized quality, and yield while enhancing regulatory compliance.

Although PAT can play a role in helping pharmaceutical executives improve efficiencies, adoption of PAT has been slow, mainly because of concerns about process validation and compliance. FDA’s PAT initiative holds great potential but it cannot, by itself, address the full scope of pharmaceutical manufacturing issues. What manufacturers will need to put in place is a connectivity technology—a system that connects all of the disparate data available in the various systems. This includes the large volumes of new continuous data from PAT instruments. A single point of real-time access by multiple users must be provided so that the data are easily available in combination with all the other manufacturing data that are collected in existing systems.

For the value of PAT to be fully realized, companies must begin paying attention to the connectivity problem between their various data-gathering systems and the real points of use for that data. But before we discuss how this can be done, we must take a close look at the current state of the pharmaceutical industry to better understand some of the drivers for change and the benefits of change, including PAT.

Federal and industry pressures on pharmaceutical manufacturing

Significant changes in the industry are forcing pharmaceutical companies to shift their focus to squeeze efficiencies out of their supply chains. These pressures include

- skyrocketing R&D costs
- rapidly decreasing periods of exclusivity
- increasing pressure from the generics marketplace

- increasing price scrutiny
- greater enforcement of current good manufacturing practices (CGMPs) from FDA.

GMPs were last reviewed by FDA in the late 1970s. During the past 30 years, FDA's involvement in regulating the industry has grown with the increase in the number of drugs that have been approved for market.

In 2002, FDA established a new enforcement precedent with the launch of systems-based inspections. In the first year, the majority of FDA's warning letters and 483 citations were directed to quality, production, and laboratory systems. One large pharmaceutical manufacturer received a \$500-million fine in 2002 for failure to meet FDA regulations. To avoid a similar fate, other manufacturers will have to step forward to take stock of their systems and implement significant improvements.

Such strong enforcement of FDA requirements has forced pharmaceutical manufacturers to examine their current processes and systems. It has become imperative that steps be taken to improve what manufacturers do with the data collected from the drug production processes to comply with regulatory requirements.

Other industry issues cause disruption to the manufacturing process. According to FDA's Janet Woodcock, director of the Center for Drug Evaluation and Research, there is an increasing incidence of manufacturing problems, which leads to the disruption of operations, drug recalls, and drug shortages. Many pharmaceutical manufacturers have failed to modernize facilities and are hesitant to innovate. Plants operate at dangerously low efficiency rates with insufficient attention to quality assurance.

In addition, pricing pressures are driving pharmaceutical companies to pay closer attention to the manufacturing process. In June 2003, President Bush signed a bill that would limit patent extensions to pharmaceutical companies and drive more competition in the marketplace. Imported drugs also create a more competitive environment when they can often be purchased for less than 50% of the cost of domestically available drugs.

Despite these realities, pharmaceutical manufacturers have continued to generously allocate funds to discovery and marketing while allocating insufficient funds

to manufacturing. Without strong manufacturing operations, many of the new drugs will produce less revenue than their full potential as a result of longer-than-necessary process start-up and scale-up times, too many lost batches, process instability and quality problems, and fines and recalls. All of these problems can be avoided.

Given all these factors, enormous pressure exists for companies to step up and improve manufacturing processes to comply with regulatory requirements in a way that improves operating efficiency at the same time. Fortunately, FDA is lending strong support by encouraging the use of PAT.

PAT benefits

FDA formed a subcommittee in 2001 that has established guidelines for the use of PAT, effectively sending a message that the agency sees great promise for PAT in addressing manufacturing compliance and operating efficiencies.

When properly implemented, PAT enables manufacturers to improve operational efficiency. Incorporating PAT into the manufacturing process can deliver significant rewards, including

- greater control of product uniformity leading to improved safety and better quality compliance
- shorter cycle and batch-release times, leading to measurable cost savings and improved supply chain stability
- movement toward parametric (real-time) release that could dramatically reduce inventory requirements and overall costs.

With its continuous data output, PAT provides manufacturers with ever-larger volumes of data that have not been available before. The large amounts of beneficial information that can potentially be obtained from these data position companies for greater success through improved compliance and operations. The potential exists to make much better data-intensive decisions.

Challenges to implementing PAT

Many companies have resisted implementing PAT because they believe things are fine as they stand today. Companies fear that if they share new data from PAT measurements, they risk exposure and

penalties from FDA even though the process may be operating correctly and producing acceptable material as determined by approved traditional measurements. Because PAT measurements can show potential flaws in processes that have previously gone unidentified, companies fear that they might then be subjected to inappropriate penalties for process flows that are not associated with any real risk to the public.

To address this issue, FDA has established a regulatory framework that gives pharmaceutical manufacturers latitude as they investigate the applicability of PAT in their manufacturing processes. Companies need not fear having their existing manufacturing lines shut down arbitrarily.

Another barrier to implementing PAT is that the return on investment will probably not be immediate—a requirement that decision makers are often asked to satisfy in today's difficult financial times. One option is to implement PAT on new processes. This option allows existing manufacturing processes to proceed as usual. Another option is to implement PAT in a limited way on an established process for observation purposes and to gain experience before full-scale implementation. This option allows manufacturers to adopt PAT in a more stepwise fashion and to demonstrate the benefits over time as they gain experience.

Without a system in place that connects the large amounts of data gathered by PAT to the point of use, in combination with the existing data-gathering systems such as the raw material and final-product quality data systems, process historians, and batch record systems, the manufacturer will fail to realize the full value that the data offer. The ability to use the data in a connected or combined way will give manufacturers much-needed insight into how to stabilize the manufacturing process that will improve the overall outcome. Connectivity will not only allow pharmaceutical and biotech companies to realize the value provided by PAT, but equally important, they will see an increased value from their existing data systems.

FDA is encouraging innovation within the industry and providing a practical regulatory framework for it. The strongest business arguments for manufacturing improvement include a decrease in com-

pliance risks, measurable reductions in cycle times and error rates, reduced costs for completing out-of-specification (OOS) investigations, and the ability to leverage existing investments in plant data infrastructure. Now is the time for pharmaceutical manufacturers to take advantage of the benefits of this type of manufacturing technology or face the increased cost of having to implement it later when

it becomes the de facto standard for the industry.

The industry technology landscape

What systems must pharmaceutical manufacturers rely on today? Most have a variety of data systems that do not provide the right kind of integrated view of the manufacturing process. The lack of integrated functionality between data systems

in manufacturing leads to a greater communication breakdown among those involved in the manufacturing process, including several key teams (e.g., quality professionals, operating staff, process engineers, and plant managers) that need to work together to drive good manufacturing outcomes.

Currently, manufacturers gather data at every step of the process. As a product stream moves through the plant, data related to the same batch are recorded in several systems. Many discrete data values are measured once per batch. Continuous data include time-series profiles stored in SCADA, DSC, and PLC systems and strip charts. Data are collected across various departments and in a variety of database systems ranging from ERP and LIMS to engineering. Paper batch records are created to capture data such as equipment records and quality records.

The main problem that exists today is that very little manufacturing and quality data can be easily accessed as an integrated whole across the process at the point of use by those involved in data-intensive decision making regarding issues such as batch release, OOS investigations, trending, and process improvement. The concept of real-time is of utmost importance here. To be useful and minimize costs, information must be available as soon as it is collected from the process instruments and assays—or at the very least in sufficient time to affect the outcome of the next batch. If data are sufficiently and easily accessible, those that are involved in investigations can potentially avoid the loss of the next batch. The reality is that in most plants today, the time that it takes to obtain and work with the necessary data, identify the problem, and find the solution is weeks to months. The result is increased compliance risks, inefficient operations, delayed time to market, and ultimately, lost revenue.

Beyond PAT

Efficient data-intensive decision making is not a common practice in today's pharmaceutical manufacturing. Companies aspire to make decisions that take into account all of the existing data, but the barrier to doing so is extremely large. The additional massive amounts of data collected via PAT and the time it takes to ac-



cess data from the various other sources will not allow for efficient decision making.

Although the joint efforts of FDA and the pharmaceutical industry in adopting PAT into the manufacturing process promise important gains in regulatory compliance and operating efficiencies, PAT alone cannot solve the many challenges that the industry faces. The lack of timely, cost-effective data availability with connectivity to the point of use may be the single largest hurdle to compliance and operating efficiencies in pharmaceutical manufacturing today.

Instead, PAT must be part of a comprehensive, manufacturing enterprise-wide solution that ensures relevant time data availability and must provide a validated environment for data-intensive decision-making. The need for technological innovations that can address the whole scope of pharmaceutical manufacturing, and not just the additional new data that PAT provides, could not be more pressing.

The opportunity to make data-intensive decisions efficiently with equal regard to

regulatory compliance and operational efficiency is not widespread in the industry. However, this situation could change for the better as new software technologies that were developed in the past few years become available in a commercially useful form built specifically for pharmaceutical manufacturing. One interesting new software technology that can fill this void is the combination of a connectivity software engine with a combined process- and data-modeling capability.

This new connectivity technology enables the data to be easily available (as soon as it is collected by the process instruments and assays) at the point of use in a decision-making environment that is useful to all members of the key manufacturing teams in a centrally administered architecture. Through a single user-centric interface with process-centric views of the manufacturing data, the connectivity technology streamlines the process of data access, conditioning and analysis, reducing the effort from weeks or months to mere minutes. With a data-intensive decision-making

environment like this, manufacturing organizations can easily accomplish a variety of compliance and operational tasks as a widespread, cross-functional habit. They can also clearly identify critical process parameters, both single and interacting.

Armed with this technology, manufacturers can confidently identify critical process drivers, effectively communicate that information to process stakeholders, and quickly make the adjustments necessary to improve compliance and operating efficiency at the same time. It is technologies such as these that enable the comprehensive data availability that PAT cannot deliver by itself. They provide the comprehensive and validated environment for data-intensive decision making through information sharing across the larger manufacturing and quality team that the industry so desperately needs. **PT**

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