PAT: It's All About Value

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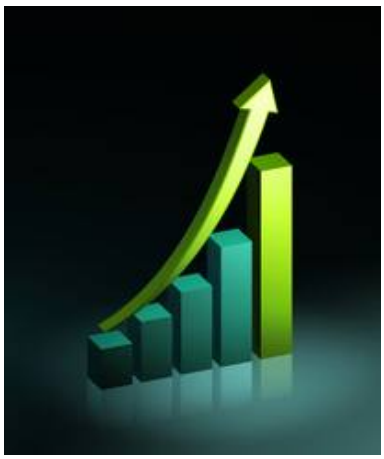
Since the inception of the FDA's PAT initiative, discussions of its implications have focused largely on the application of on-line instrumentation. But a technology-first approach to PAT misses the real point: business value.



One of the founding principles of the PAT initiative, stated by Ajaz Hussain, the FDA's Deputy Director, Office of Pharmaceutical Sciences, is to improve process understanding. Improved process understanding enables manufacturers to determine precisely where the greatest risks and opportunities lie in their operations and strategically address them – not simply throw technology at them. Instead of incrementally improving unit operations that, in isolation may have little effect on overall process performance, you can cost-effectively deploy PAT where it will do the most good to improve quality, consistency, throughput, and speed to market – in other words – to increase value. Such a value-first approach to PAT entails some simple, but powerful, principles;

Diversify your PAT program to include products in both development and manufacturing – where there is business benefit to be gained.

Although the PAT initiative initially appeared to focus on applications in drug development, the FDA is also encouraging the use of PAT strategies for the manufacture of currently approved products. In both instances, the focus should be on value: (1) maximizing the probability that a product in development will make it to validation, scale-up, and technology transfer with minimal glitches and (2) optimizing current manufacturing processes to lower costs, increase productivity, and lower compliance risk. Just as you would diversify an investment portfolio, diversify your PAT investment to ensure both near-term and longer-term value.

Extract near-term value from PAT by reducing the total cost of quality (TCOQ) in production.

In the world of manufacturing, the typical total cost of quality – that is, all of the costs incurred as a result of poor quality – eat up as much as 20-30% of sales. For a $1 billion pharmaceutical company that would amount to a whopping $200-300 million annually. Most companies incur such high costs because their quality management systems are designed to detect poor quality, not prevent it in the first place. But with PAT, it's back to the future: the aim is to build in quality up front, as quality pioneer W. Edwards Deming urged decades ago, not inspect it in after the fact. And, as Deming and other quality visionaries understood, the way to build in quality and translate it into value is to understand processes and improve them, not simply adopt new technology.

Processes that stand at 2.5 sigma yield a reject rate of approximately 2 percent. Compare that with processes that stand at six sigma, which means an infinitesimal reject rate of about 3.4 parts per million. By closing that gap with quality management systems and manufacturing controls that focus

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critical points in a process, you can optimally apply your resources at the right place, the right time, and to the right things. The result: dramatically reduced TCOQ that translates into immediate bottom-line benefits.

Extract long-term value from PAT by achieving quantum leaps in development cycle time.

Reducing TCOQ by reducing variation in production processes is only half of the PAT value equation. The other half: accelerating speed to market with products in development. This is accomplished by application of state-of-the-art qualitative and quantitative techniques for process characterization and control such as multi-variate

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analysis, C_{pk}, design of experiments, regression, and others. This approach can dramatically increase the efficiency and effectiveness of the drug development process, resulting in quantum improvement in development cycle time and far greater return on investment through longer patent protection and first-to-market advantage.

Interestingly, some generic and small pharmaceutical companies have made significant strides in PAT because, paradoxically, implementation of PAT is not the goal. They focus on attaining process understanding quickly and efficiently, resulting in rapid product development cycle times and generating much-needed revenue. Smaller, leaner organizations are also more apt to think cross-functionally and in an integrated fashion. By harnessing PAT to value, they apply it more judiciously, rapidly, and cost-effectively than some larger companies.

Focus your PAT implementations on the entire process train for those products that have the most potential to improve your business performance – don't just focus on individual points in many processes.

With limited resources, companies that choose to implement PAT one unit operation at a time (e.g. blending or granulation) rather than one product at a time may be sub-optimizing the potential benefits from their PAT initiative. Although focusing on a particular unit operation across many products may improve process understanding and productivity at that step, the bottleneck in the process is likely to shift to another process step. In such cases, it is possible that you will neither speed time to batch release nor be in a position to pursue online batch release in the future.

Focus on identification and prioritization of critical to quality (CTQ) process parameters.

All parameters are not created equal. To make good use of scarce company resources, apply process analytical technology and improve process understanding for those parameters that are key drivers of variation in critical release parameters. You will thereby lower PAT implementation costs and significantly increase return on your PAT investment. However, you must be able to answer some key questions (1) Can you account for greater than 85% of the process variation in critical release parameters with the parameters you are currently measuring in the batch record? (2) Which of those parameters is critical to quality? (3) If you can account for only 80% or less, what are the CTQ parameters that you are not currently measuring?

For example, out of some 150 possible variables in a time-release, solid-dose drug, there may be only five key parameters that need to be fully understood and controlled (e.g. mixing speed and position of mixer, raw material particle size, etc.) These critical process parameters should

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be primary candidates for the application of PAT.

Such CTQ parameters should be identified through a structured investigative process that begins with a qualitative analysis and then leads to a quantitative, statistically- based methodology that includes the use of such tested techniques as multi-variate regression analysis and design of experiments. Once you have identified the critical-to-quality (CTQ) parameters – not just proxy measures – you are on your way to applying PAT in the most value adding and cost-effective fashion.

Apply analytical technology to improve process understanding.

Some companies are under the mistaken impression that they are "doing PAT" if they replace manual or low-technology data collection techniques with high-technology automated approaches. Again, the goal of PAT is to enhance process understanding, process control, and product manufacturability. Although automating data collection might be worthwhile for other reasons, it does not necessarily represent a PAT application. The technology-first approach to PAT, on occasion, mistakenly seeks to automate data collection without first understanding the process holistically and then determining which parameters are critical and how the application of the analytical technology will augment the level of process understanding.

Involve manufacturing early in the development process.

Although this principle is a self-evident truth, surprisingly few organizations adhere to it. In the siloed cultures of some pharmaceutical companies, drug development and technical services personnel often believe that the manufacturing people don't fully understand the issues and that their lack of understanding only slows drug development. By delaying, or minimizing, the involvement of manufacturing personnel, the development and technical people sincerely believe that they're optimizing the development process. In fact, they're improving the efficiency only of their part in it while sub-optimizing the whole. PAT offers an opportunity to foster the integration of the development and manufacturing processes within your company, not only to ensure greater manufacturability of products and accelerate speed to market, but also to establish a mechanism for continuous improvement in your operations.

Design a PAT management process that encourages cross-functional integration and communication. Don't simply staff a PAT project – integrate the right skills sets and link them to business processes and financial outcomes. That means breaking down the silos that typify most pharmaceutical organizations and structuring a PAT initiative around value, not purely operational or technological outcomes. The vision must come with the strong commitment of leadership, and the strategy must be translated into processes, operating procedures, and behaviors that can be measured and sustained. Further, the connection between those measures and financial measures must be made explicit, clearly communicated, and used to guide activity across the organization.

Effective PAT initiatives begin with an appreciation for the value they can bring, proceed on the basis of process understanding, and succeed through the thorough integration of both.

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