White Paper

PAT Initiative Expected to Invigorate Pharmaceutical Industry with Improved Quality, Better Efficiency and Improved Profits.

The implementation of Process Analytical Technology (PAT) is bringing real-life benefits and improvements to many pharmaceutical processes. This white paper takes a detailed look at the business drivers of PAT – regulatory and financial – and highlights the fundamental steps to successful implementation. The benefits are lower production cycle times, improved manufacturing efficiency, reduced rejects and increased production uptime.

Introduction

As the United States' manufacturing sector emerges from one of its most challenging decades in recent memory, pharmaceutical manufacturers are taking a closer look at how they can continue to produce the highest quality products and at the same time generate profit. In addition, the pharmaceutical industry as a whole – with encouragement from the FDA – is seeking to accelerate the pace of manufacturing innovation to meet ever-increasing cost, efficiency and time-to-market demands. While pharmaceutical manufacturers continue to generously allocate funds to research and marketing, the industry as a whole lags behind other automated industries in one key aspect: manufacturing quality analysis.

To that end, there is growing enthusiasm in the industry for the many potential gains offered by process analytical technology (PAT), a new FDA initiative that aims to foster improvements in manufacturing efficiency and product quality while creating a harmonization of regulatory expectations. PAT provides a framework for designing, analyzing and controlling manufacturing through timely measurements of raw and in-process materials to help ensure desired product quality. The PAT initiative focuses on the principles of building quality into the product and process, as well as continuous process improvement.

The goal of PAT is to encourage the industry to adopt innovative technologies to increase quality without raising concern that a new approach will lead to validation risks and production delays. The key components of this knowledge-based approach are better understanding of the product manufacturing process, data analysis, process analytical tools, process monitoring, and continuous feedback during the manufacturing process.

Experience indicates that the highest performing organizations are rigorous about their processes, especially as they relate to better understanding of manufacturing operations, process control, validation and ongoing commitment to quality improvement. With an emphasis on process understanding, the PAT initiative is designed to allow companies to determine what variables are most critical to the final desired product; where controls should be inserted into the process; and what factors control sample degradation. In this context, process understanding refers to ensuring that sources of variability are identified and explained, variability is managed by the measurements of the process and product quality can be predicted.

The underlying premise of PAT is that quality cannot be tested into products; instead it should be built-in or should be by design. By encouraging the application of advanced analytical technologies and improvements in manufacturing efficiency, companies hope to parlay this strategy into higher quality products, less rework, increased profits and a distinct competitive advantage.

Industry Drivers

A key driver of PAT comes from the regulatory side, where the FDA recognized that its traditional approvals procedures were actually hindering manufacturing innovation. With increased guidance and assurance from the FDA, PAT is expected to encourage innovation and to reassure manufacturers that moving toward PAT-based manufacturing is in their best interest. While the benefits are clear, the hesitation toward adopting PAT is not without reservations.

Of specific concern is the fear of FDA reprisals should companies implement PAT on existing processes only to find problems in the system that wouldn't have been discovered in normal process monitoring. The FDA recognizes this concern and is working to alleviate manufacturers' fears, as noted in the FDA's draft guidance document for PAT: "FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool. FDA's routine inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods)."

Another important driver for PAT is the pressing need within the industry to reduce production costs and speed time-to-market. Pharmaceutical companies have historically taken a conservative approach when it comes to implementing process changes and upgrading technology. But business models are changing and the importance of manufacturing's role in the financial performance of pharmaceutical companies is increasing. While the cost of restructuring production lines may be daunting to smaller companies, the savings gained from more efficient use of resources, reduced waste, faster product approvals and a lower risk of product recalls more than outweigh the cost to implement PAT.

A Change in Strategy

The traditional approach to regulating quality in pharmaceutical manufacturing involved a laboratory analysis to verify quality after manufacturing the finished product. Many of these inefficiencies are based on traditions, cost considerations and a general reluctance to change. The disadvantages of this approach are continual process optimization, high levels of rejected product and limited adoption of new technologies.

The key to the success of PAT is applying the process monitoring tools needed to analyze each of the critical product attributes. Equally important is having the process controls in place to make production adjustments based on the analysis. Detecting errors or process deviations and correcting them while the product is being made is more cost-efficient, and can help justify flexible regulatory paths for innovations in manufacturing and post-approval changes.

The pharmaceutical industry has historically been lab-centric – with minimal closed-loop, real-time control and limited enterprise-wide data availability. A key to optimizing manufacturing in the future will be to make data visible in the context it is needed. Similarly, the ability to cost-efficiently manage data with connectivity to the point of use will be important both within the company and with the FDA as part of the approval process.

For example, one of the prominent techniques of PAT is online monitoring, which means it's not only recording information, but it's also closing the loop and making adjustments to the process as the product is being manufactured. In other words, the ability to analyze the production stream is pointless if you can't respond to what the results are telling you.

In today's environment of open-system architecture, access to data is becoming less of a challenge. However, legacy systems persist, and the underlying technology of the legacy system often does not support the open-system philosophy. Fortunately, control system vendors and third-party support companies have developed communication drivers in support of industry standard communications for many of the older control system platforms.

To provide consistency and seamless connectivity to the enterprise, many pharmaceutical companies are turning to technology suppliers like Rockwell Automation for single, integrated platforms. These modular, scalable and open platforms help reduce lifecycle costs while assisting manufacturers with ever-changing compliance regulations.

Steps to Implementation

While the emergence of PAT is not new, it does require a shift in organizational structure, including the development of in-house expertise and training; changes to existing inspection and validation methodologies; and reliance on specialized PAT support teams. The implementation of a PAT program requires identifying the relevant technologies that can be applied and the creation of an integrated data management infrastructure capable of handling the volume of data to be recorded. It also requires advanced automation, visualization and analysis tools to manage the continuous identification and prediction stages in the process.

For the majority of manufacturers, the transition to a PAT strategy is too monumental to be made in a single effort. Instead manufacturers should look to implement PAT programs in phases, starting with a specific project or production line and then gradually expanding to other areas. The first step is to conduct a productivity improvement appraisal (PIA) to analyze existing product lines and determine those that may benefit most from PAT. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, systemic, control and risk analysis conducted in an integrated manner.

A PIA report identifies possible productivity improvement opportunities such as:

- identification of best practices
- identification of acquired critical operating data (COD)
- reusable engineering components
- cost reduction
- overall equipment effectiveness (OEE) data
- and other key performance indicators (KPIs)

Potential costs and benefits can then be generated, which will help create a list of financially viable projects. By carefully analyzing likely opportunities and implementing PAT projects in phases, companies more accurately assess the potential impact of process changes while managing investment costs. Defining the business drivers and potential benefits from a PAT initiative are essential for a successful project. This effort also will establish the framework for continuous quality improvement. Risk assessment, change management systems and a process monitoring plan are created during this effort to establish the importance of the investment strategy.

Once a specific project is identified, the next step – discovery phase – involves re-evaluating work practices, process chemistry, manufacturing techniques, and inspection and validation methods. New products are one area where companies are concentrating their efforts and activities. Products with recurring quality issues are other good candidates, because process deviations or exceptions often result in lost or poor product quality leading to higher costs, especially with expensive and hard to acquire raw and intermediate materials. Management of processes by operators not fully understanding the process is another issue prompting analysis. Partial PAT adoption is suitable for processes which can benefit from new technology to correct or prevent a problem in the production process.

In the analysis phase, engineers perform a thorough and systematic review of product filings, exception history, manufacturing and quality data and other sources for each product to verify if the original critical process parameters (CPPs) are still valid, or whether other parameters not originally identified are now more critical. The emphasis is on CPPs that affect in-process product quality rather than quantitative measurements. The analysis also involves looking at the critical operator data (COD) necessary and/or for integrated system control or required by an operator to effectively manage the process.

The identification and confirmation of CPPs is accomplished by using neural net, mathematical modeling and statistical software to find correlations between key quality attributes and measured real-time process parameters. By using real-time methods, the process endpoint no longer needs to be a fixed time, but rather can be the time required to reach a specific state or condition.

The definition, analysis, and documentation of CPPs require competent engineering and compliance expertise. Activities include:

- preparation of a formal project plan; submit for approval
- identification and setup of toolsets necessary for project implementation
- identification of product process specifications and limits
- identification of at-line or in-line or on-line process controls and tests
- acquisition of necessary information and data
- analysis of data
- preparation and delivery of a CPP analysis report
- assessment report, which includes high-level recommendations for improvement
- preparation and delivery of productivity improvement appraisal (PIA)

The results of the analysis provide the basis for determining which manufacturing technologies and quality assurance tools will comprise the PAT solution. This might include: data acquisition and analysis technology; modern process analyzers or process analytical chemistry tools; knowledge management systems; and process and endpoint tools for real-time or near-real time monitoring and control of all critical attributes. It's important that the risk and impact assessments be completed on the basis of data and not on opinions or theories.

Design strategies should address:

- the attributes of input materials
- the ability and reliability of process analyzers or other instrumentation like NIR sensors to measure critical attributes, and
- the achievement of pre-established process endpoints to ensure consistent quality of the output materials and the final product.

Keep in mind that improperly developed processes, poorly trained operators, or equipment that has not been properly qualified will hinder any PAT efforts. The key to long term success in applying PAT is oversight after installation by a specialized, dedicated PAT support team. To that end, it's critical that companies obtain and retain employees with education, training, and experience in multiple disciplines, including process control engineering, process analytical chemistry, instrumentation and metrology.

Organizations also can benefit by relying on the knowledge and expertise of an outside consultant. First, they need to review their engineering and analytical resources and determine if these are areas that should be managed in-house, or whether they could be optimized and managed more effectively with outside assistance. For example, Rockwell Automation provides global consulting, engineering and support services that can help with integrated PAT solutions and can be rolled out throughout the organization with fully documented and well-defined functionality of systems and procedures. This results in ease of validation and maintenance, helping to assure that financial return is long-lived and sustainable.

Rockwell Automation service offerings include:

- program and project management
- consulting
- analysis
- hardware and software implementation
- system integration

Documenting Benefits

Also key to successful implementation is the ability of project managers to make a solid business case for adopting PAT. A good first step is to educate management on the value of PAT, which requires effectively articulating – in management terms – what the PAT initiative is intended to accomplish and how this relates to the underlying business goals.

For example, how does the need to improve manufacturing quality relate to the overall organizational goal? When making the case, it is vital to stay objective, keep emotions out of the discussion, stick to the facts and understand the business trends that drive the need for the request.

When providing specifics on the activities and tools, continue to relate the anticipated results back to the business drivers as they pertain to management goals and customer demands. For example, how will a new process instrumentation system help increase line speeds, reduce quarantine times and reduce expenses related to scrapped batches? More specifically, how does this impact productivity and product yields – two key management goals?

While some companies are proceeding with PAT initiatives, rather than traditional analyses, to introduce new complex and expensive compounds, others are using traditional approaches along with PAT initiatives so that accurate comparisons can be obtained from multiple points of view. Typically, these dual projects are used with existing products that have a wealth of historical data. Successful projects can help validate the qualitative results of the PAT-based systems against existing systems that already have regulatory approval. The major thrust is to work collaboratively with the FDA for new product developments and scale-ups as the FDA has offered incentives, such as changes without prior approval that result in higher quality products produced faster and at less cost.

One Step at a Time

The underlying goal of PAT is to ensure that processing time or work cells are optimized and that the final product really conforms to established standards. By making carefully planned investments in process analytical tools, control systems and equipment, more instrumentation and resources, companies can show measurable results to senior management. Validation, which is a life-cycle activity, when based on PAT results may be achieved with less time, resources and facility startup time. This may yield a new facility or production line coming on-line sooner with diminished issues. With tangible benefits in hand, they can build credibility and better positioned themselves to justify larger investments and expand the program on an incremental basis. The reality is that good manufacturing techniques will always reduce a plant's total cost to produce.

Gains in quality safety and/or efficiency will vary depending on the product and are likely to come from:

- reducing production cycle times by using on-, in-, and/or at-line measurements and controls
- improving efficiency by managing product variability
- reducing rejects, scrap, and re-processing
- considering the possibility of real time release
- increasing automation to improve operator safety and reduce human errors
- facilitating continuous quality enhancements that yield positive relationships with regulatory agencies.

Gaining an Edge

In today's lean manufacturing environment, it's critical for companies of all sizes to focus on optimizing their production processes. By adopting the PAT framework and building in quality on the front end, pharmaceutical manufacturers can more effectively maximize their production assets and will be better positioned to adapt quickly to market changes. Moreover, since the initiatives have the support of regulatory agencies, a successful PAT initiative can lead to regulatory incentives. Besides, it's better to be ahead of the curve than behind it.

For more information, go to www.rockwellautomation.com/lifesciences

www.rockwellautomation.com **www.propack-data.com**

Corporate Headquarters:
Rockwell Automation, 777 East Wisconsin Avenue, Suite 1400, Milwaukee, WI, 53202-5302 USA, Tel. (1) 414 212 5200, Fax (1) 414 212 5201

Headquarters for Allen-Bradley Products, Rockwell Software Products and Global Manufacturing Solutions
Americas: Rockwell Automation, 1201 South Second Street, Milwaukee, WI 53204-2496 USA, Tel. (1) 414 382 2000, Fax (1) 414 382 4444
Europe/Middle East/Africa: Rockwell Automation SA/NV, Vorstlaan/Boulevard du Souverain 36, 1170 Brussels, Belgium, Tel: (32) 2 663 0600, Fax: (32) 2 663 0640
Asia Pacific: Rockwell Automation, Level 14, Core F, Cyberport 3, 100 Cyberport Road, Hong Kong, Tel: (852) 2887 4788, Fax: (852) 2508 1846

Headquarters for Dodge and Reliance Electric Products
Americas: Rockwell Automation, 6040 Ponders Court, Greenville, SC 29615-4617 USA, Tel: (1) 864.297.4800, Fax: (1) 864.281.2433
Europe/Middle East/Africa: Rockwell Automation, Herman-Heinrich-Gossen-Strasse 3, 50858 Köln, Germany, Tel: 49 (0) 2234 379410, Fax: 49 (0) 2234 3794164
Asia Pacific: Rockwell Automation, 55 Newton Road, #11-01/02 Revenue House, Singapore 307987, Tel: (65) 6356 9077, Fax: (65) 6356 9011

Headquarters for Propack Data Products
Europe: Rockwell Automation Propack Data GmbH, Vincenz-Priessnitz-Str. 1, 76131 Karlsruhe, Germany, Tel. (49) 721 9650-6, Fax (49) 721 9650-888, propack-data@ra.rockwell.com
Americas: Rockwell Automation Propack Data, 2000 Regency Parkway, Suite 675, Cary, NC 27511 USA, Tel. (1) 919 465 1741, Fax (1) 919 465 1742
Asia Pacific: Rockwell Automation, 55 Newton Road, #11/02 Revenue House, Singapore 307987, Tel. (65) 6356 9077, Fax (65) 6356 9011

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