Review Article

Process Analytical Technology (PAT): A Real Time Quality Assurance

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ABSTRACT

Process Analytical Technology (PAT) promise to deliver a bigger, brighter future in terms of encouraging "the voluntary development and implementation of innovative pharmaceutical development, manufacturing and quality assurance"[1] while ensuring patient safety and increasing profitability for the life sciences industry. No matter how you slice it, reducing raw material and batch losses, preventing scraps and rejects, insuring real-time release of product, increasing safety through the proliferation of automated manufacturing and facilitation of continuous process improvement through management of variability and improved efficiencies can lead to better product quality, enhanced consumer safety and increased profitability. It promises to be the most radical change in pharmaceutical manufacturing in 30 years. It's actually a part of the US Government FDAs' 21st century initiative, built into its strategic plan & supported by Presidential Executive order 13329- encouraging innovation in manufacturing. The scope of this article is to introduce the reader to PAT. It, however, is a wide-ranging subject, which is expanding rapidly.

Keywords: critical control parameters, in-line, at-line, off-line, PAT tools.

INTRODUCTION

The term "Process Analytical Technologies (PAT)" has been used to describe "a system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical process parameters and critical quality attributes for raw and in-process materials and also processes with the goal of ensuring final product quality"[2]. The concept actually aims at understanding the processes by defining their CPPs, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing while at the same time reducing over-processing, enhancing consistency and minimizing rejects. The FDA has outlined a regulatory framework[1] for PAT implementation. With this framework – according to Hinz[3]– the FDA tries to motivate the pharmaceutical industry to improve the production process. The PAT initiative focuses on building quality into the product and manufacturing processes, as well as continuous process improvement.

"Pharmaceutical manufacturers have continued to generously allocate funds to discovery and marketing, while allocating insufficient funds to manufacturing," says Justin Neway, executive vice president and CSO of Aegis Analytical Corp. "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." On the R&D side of the pharmaceutical coin, modern drug discovery includes a wide variety of automated and integrated technologies, ranging from organic synthesis to spectrometric and chromatographic systems to *in vitro* and *in vivo* testing systems. On the manufacturing side, however, innovation seems to move more slowly, and manufacturers are being asked to rely on processes that have remained largely unchanged for the past 30 years. Because it is a less mature field than many other manufacturing industries such as petroleum or automobile, regulators decided that pharmaceutical production needed guidance to develop more effective methods of analysis. This decision is the driving force behind the PAT initiative.[4]

PAT is a term used for describing a broader change in pharmaceutical manufacturing from static batch manufacturing to a more dynamic approach. It involves defining the Critical Process Parameters (CPPs) of the equipment used to make the product, which affect the Critical Quality Attributes (CQAs) of the product and then controlling these CPPs within defined limits. This allows manufacturers to produce products with consistent quality and also helps to reduce waste & overall costs. This mechanism for producing consistent product quality & reducing waste presents a good case for utilizing continuous manufacturing technologies. The control of a steady state process when you understand the upstream & downstream effects is an easier task as common cause variability is easier to define and monitor. PAT (also referred to as in situ analytics) tools are heavily applied in pharmaceutical workflows that underpin drug substance and dosage form development, scale-up, and manufacture. Even in this current state, industry has not attained the FDA's full vision of PAT, described as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" for a significant number of products on the market or in development.

The need for industry to attain this PAT vision is heartily discussed and debated within companies, conferences, and social media. Nevertheless, to ensure product quality, industry identifies and implements controls [often, using a Quality by Design (QbD) approach to identify and mitigate risks], irrespective of the type or location of the analytics and controls, or whether additional cost benefits could be achieved using in situ analytics and real time control.

Internal and external impediments can be encountered when considering and recommending the use of in situ analytics for control purposes in commercial manufacturing. Internal barriers include uncertainty related to return on investment (equipment and employee efforts), staff skills, and capabilities, hardware equivalence between the development and manufacturing sites, and integration of PAT equipment into the manufacturing site's quality management system. External barriers include vendor incompatibilities (e.g., challenges of integrating, into a single PAT system, hardware and software from different suppliers), and regulatory challenges (such as the country or region specific expectations and guidance's).[11] Many products are developed and filed for global markets, and these differing regulations and requirements can result in inefficiencies such as having to test the same product to multiple standards (specifications) using multiple test procedures, along with the development of conventional off-line reference methods.[5]

What Is PAT?[5]

In the FDA's PAT definition, "analyzing" equates to in situ analytical tools, and it includes many measurement and instrument types, e.g., thermocouple, pH probe, vibrational spectroscopy (mid-infrared, near-infrared, Raman, ultraviolet), mass spectrometry, chromatography, focused beam reflectance measurement, and nuclear magnetic resonance. Just as there is no single off-line analytical tool that meets all process development understanding or control strategy needs for a product, there is no one in situ analytical tool that will work for all applications. Indeed, for some types of chemistry, in situ tool use is challenging at best, and sampling and off-line testing may be desired. As such, PAT tools are just one set of analytical technique to consider when determining which analytics are appropriate for process and product understanding, monitoring, and control. The appropriate analytical techniques for the process or product are determined based upon chemistry, stage of development, technique availability (in development and at the manufacturing site), process equipment accessibility, and configuration, personnel skill sets in the technique, and regulatory acceptability. PAT data may measure chemical or physical aspects. It may be univariate, multivariate, raw, or mathematically preprocessed. Temperature, pressure, and flow measurements are often not considered PAT tools (as these measurements have been routinely made for decades). However, through process understanding, such fundamental measurements may be directly correlated with a critical quality attribute (CQA) and used as a parametric control measurement for process control purposes.

Table 1 describes high level differences between PAT used in development (used to develop process understanding) and manufacturing (based upon process understanding and used as a control strategy).

Table 1: Basic Contrast between PAT in Development and Manufacturing

	Development	Manufacturing
Overall Purpose	Understand	Control, trend analysis
Desired Technology	Multicomponent analyzers	Targeted analyzers
Data Complexity	Multivariate	Univariate or multivariate[a]
Support Requirements	High level expertise-continuous support	Robust and automated-minimal support
Quality System	Development mode	GMP
PAT Expertise	Method design and development	Operation and maintenance

[a]While univariate analysis is preferred for simplicity, PAT tools such as spectrometers will often require multivariate analysis.

Why Use PAT?[5]

Many process parameters may be measured by standard off-line techniques. However, PAT provides more frequent and automated measurements, enabling the study of kinetic processes as well as expanding capabilities for automated, real time process control. More importantly, the technology can provide measurements of parameters that are difficult or undesirable to measure with standard off-line techniques (e.g., highly hazardous materials, high pressure systems, high or low temperature systems, transient intermediates, and heterogeneous systems). One of the greatest challenges to understanding complex physical and chemical processes is the ability to measure process components with a minimum of perturbation (for both the measurement and the process). The foundation of PAT, whether it be applied in R&D or manufacturing, is the measurement.

In R&D, reliable measurements can reveal previously unknown process components, mechanisms, and relationships between variables, leading to the development of predictive models-both mechanistic and chemometric. These predictive models can be both qualitative and quantitative in nature, and the desired goal is to predict process outcomes. As development progresses, the cumulative information is used to map the process design space and to develop a control strategy for maintaining the process within that space. Thus, PAT is used during every phase of development

(preclinical through commercial manufacturing) and is a valuable set of analytical tools for the pharmaceutical scientist to interrogate processes.

Unit Operation or Process Step	In-Line, At-Line, Off-Line Technique
Raw Materials, Dispensing	NIR, Raman, Particle Size
Reaction Monitoring	mid-IR, NIR, UV-visible
Crystallization	mid-IR, NIR, Raman, FBRM, PVM
API Drying	NIR
Nano milling	NIR
Wet Granulation	NIR, FBRM, PVM, Acoustics, Particle Imaging
Compounding Tank	NIR, Raman, FBRM
Fluid Bed Drying	NIR
Blending	NIR, NIR Imaging, Raman, LIF
Lubrication	NIR, LIBS
Compression	NIR, Raman, NIR Imaging, LIBS, Terahertz, LIF
Coating	NIR, LIBS, Terahertz
Roller Compaction	NIR, Pressure Sensors, Particle Size
Hot Melt Extrusion	NIR, Raman, UV/Vis, Fluorescence
Spray Drying	FBRM
Packaging	Reflectometry
Adjuvants	Turbidity
Fermentation	mid-IR, NIR, Sensors
Freeze Drying/ Lyophilization	NIR, Raman
Chemo-metrics software	SIMCA, Unscrambler, MATLAB
Integrated data network	Siemens SIPAT, SynTQ, ABB xPAT, Symbion
Reference methods	HPLC, GC, Karl Fischer

In the early phases of development, the analytics needed for developing an understanding and definition of the process may be complex. Analyzers may be multivariate, allowing the researcher to monitor the formation and fate of multiple process components. As the process is defined and understanding is gained through these measurements, the number of parameters suspected to be critical can be reduced. As the process approaches manufacturing readiness and the process parameter control limits are established, the desire is to simplify the monitoring and control technology as much as is practical. In the ideal case, the results from advanced PAT are correlated with simple manufacturing measurements (e.g., time, temperature, pressure, and flow) to control the process. Even in these instances, PAT may be installed in the manufacturing process to obtain information for process scale-up, optimization, transfer, fault detection, and building a process fingerprint for advanced trending and controls or to understand unexpected process deviation events post mortem, and it may be included in regulatory submission documentation. Key benefits of QbD and PAT use during development include improved process understanding, and identification of critical process parameters and critical product quality attributes (and their relationships with each other). Further, to ensure product quality, this knowledge can be used for process control (in real time, if required, using advanced PAT or simple manufacturing measurements). The PAT measurement may be quantitative or qualitative in nature, and it will depend upon the application. This is a key point on how industry practically develops, analyzes, and controls processes.

How PAT works?[6]

In order to successfully implement PAT, a combination of sequential steps is essential.

First, a unit operation or process must be defined as requiring PAT or being amenable to PAT deployment. In many cases, a thorough lab-scale feasibility evaluation of analytical methods is conducted to determine which techniques may have adequate sensitivity and selectivity. Additionally, PAT goes through extensive cost-benefit analysis as to which approach may reach the production floor.

Second, a suitable PAT technique needs to be chosen which would allow for measurement of the critical process parameter (CPP), preferably in an in-line or at-line manner. The first step away from off-line laboratory testing would be at-line testing, which moves process dedicated testing equipment to the production line. One approach of PAT is on-line testing, which draws samples and monitors periodically. Another mode is in-line testing, which places probes in constant contact with the drug product. The advantage of on- or in-line testing is better control because the analysis provides the most up-to-date snapshot of the process. Near infrared (NIR) spectroscopy is one of the most routinely used techniques and has gained wide acceptance. NIR is a rapid, nondestructive technique that eliminates the need for sample preparation and enables real-time monitoring.

Next, logistical constraints would need to be considered, such as how to interface the PAT technique with the process, such as whether the equipment had applicable NIR fiber optic probe-interface ports or if modifications were necessary.

Finally, the PAT method would need a reference method for correlation of spectral data versus a traditional method value. In many instances, such as in-line content uniformity, HPLC data is correlated to NIR spectral data in order to build an accurate PAT model.

In order to generate a spectral model, chemometric software is utilized to analyze spectral data in comparison to known reference values. The PAT technique and associated models are continually updated, verified and validated. While NIR has gotten most of the attention, PAT is not limited to NIR but can include many other forms of monitoring, such as Raman, Mid-IR, acoustic

emission signals, and other imaging techniques. These are performed in coordination with qualified and validated process analyzer hardware, operating software and chemometric data analysis package. The implementation of PAT will vary widely depending on the production technology or unit operation as well as technical hurdles of the available technology. Table 1 lists common pharmaceutical unit operations and applied PAT techniques.

Commonly applied PAT techniques to Pharma unit operations

(NIR = Near Infrared; FBRM = Focused Beam Reflectance Measurement; PVM = Particle Vision Measurement; LIF = Laser Induced Fluorescence; LIBS = Laser Induced Breakdown Spectroscopy; LIF = Laser Induced Fluorescence; HPLC = High Performance Liquid Chromatography; GC = Gas Chromatography; LOD = Loss on Drying) Figure

PAT Tools:{}

There are many current and new tools available that enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. In the PAT framework, these tools can be categorized according to the following;

1. Multivariate data acquisition and analysis tools

2. Modern process analyzers or process analytical chemistry tools

3. Process and endpoint monitoring and control tools

4. Continuous improvement and knowledge management tools

Multivariate data acquisition and analysis tools

From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many different development strategies that can be used to identify optimal formulation and process conditions for these systems. The knowledge acquired in these development programs are the foundation for product and process design. Some manufacturers use multivariate mathematical approaches, such as statistical design of experiments, response surface methodologies, process simulation, and pattern recognition tools, in conjunction with knowledge management systems.

The applicability and reliability of knowledge in the form of mathematical relationships and models can be assessed by statistical evaluation of model predictions. Methodological experiments (e.g., factorial design experiments) based on statistical principles of orthogonality, reference distribution, and randomization provide effective means for identifying and studying the effect and interaction of product and process variables. Traditional one-factor-at-a-time experiments do not effectively address interactions between product and process variables. Interactions essentially are the inability of the one factor to produce the same effect on the response at different levels of another factor. Experiments conducted during product and process development can serve as building blocks of knowledge that grow to accommodate a higher degree of complexity throughout the life-cycle of a product. Information from such structured experiments support development of a knowledge system for a particular product and its processes. This information, along with information from other development projects, can then become part of an overall institutional knowledge base. As this institutional knowledge base grows in coverage (range of variables and scenarios) and data density, it can be mined to determine useful patterns for future development projects. These experimental databases can also support the development of process simulation models, which can contribute to continuous learning and help to reduce overall development time.

Modern process analyzers or process analytical chemistry tools

Process analytical chemistry as a discipline has grown significantly during the past several decades, due to an increasing appreciation for the value of collecting process data during production. From the simple process measurements such as pH, temperature, and pressure, modern tools that measure chemical composition and physical attributes have evolved. These modern process analysis tools provide nondestructive measurements that contain information related to both physical and chemical attributes of the materials being processed. These measurements can be performed in the following manner:

- Off-line in a laboratory
- At-line in the production area, during production close to the manufacturing process
- On-line where measurement system is connected to the process via a diverted sample stream; the sample may be returned to the process stream after measurement
- In-line where process stream may be disturbed (e.g., probe insertion), and measurement is done in real time
- Noninvasive, when the sensor is not in contact with the material (e.g., raman spectroscopy through a window) in the processor, the process stream is not disturbed

Process and endpoint monitoring and control tools

Following steps can be included for design and optimization of drug formulations and manufacturing processes within the PAT framework:

- Identify and measure critical material and process attributes relating to product quality
- Design a process measurement system to allow real time or near-real time (e.g., on-, in-, or at-line) monitoring of all critical attributes
- Design process controls that provide adjustments to ensure control of all critical attributes
- Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes

Therefore, it is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical quality attributes. Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state. Strategies should accommodate the attributes of input materials, the ability and reliability of process analyzers to measure critical attributes, and the achievement of pre-established process endpoints to ensure consistent quality of the output materials and the final product. Within the PAT framework, a process endpoint need not be a fixed time, but can be the achievement of the desired material attribute. This, however, does not mean that process time is not considered. A range of acceptable process times (process window) is likely to be achieved during the manufacturing phase and should be evaluated, considerations for addressing significant deviations from acceptable process times should be developed. Process end points intended for use in real time release should be considered more critical than those that are only used for in-process control.

Continuous improvement and knowledge management tools

Continuous learning through data collection and analysis over the life cycle of a product is important. Data can contribute to justifying proposals for post-approval changes including introduction of new technologies. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the regulatory agency.

The PAT Vision for Pharmaceutical Companies[8]

From R&D to Manufacturing

The Process Analytical Technology vision for pharmaceutical companies is radical. It foresees an industry that moves away from a rigid validation-based manufacturing paradigm, often bordering on an art form, to a science and engineering based approach to understanding processes, understanding and mitigating risks to poor product and leading to increased process quality.

As a regulatory framework, PAT will encourage the rapid development and implementation of innovative pharmaceutical manufacturing and quality assurance Practices.

In R&D and product development, PAT tools will be used to gain greater understanding of the chemistry and physics of the manufacturing process, enabling tomorrow's new products to move into the market faster and easier with more effective and efficient processes.

In routine manufacturing, PAT will enable continuous and real-time quality assurance to ensure consistently high product quality and performance, batch after batch.

Main Pharmaceutical Business Benefits from PAT

In Pharmaceutical R&D

• A deeper scientific and engineering understanding of manufacturing processes

• Reduced product development times, more robust licensing packages, faster scale up, and faster Time-to market for new products.

• Implementation of innovative manufacturing and quality strategies

In Pharmaceutical Manufacturing

• Reduced waste, right-first-time manufacturing, higher production asset utilization

• Real-time quality assurance and validation

• Movement toward real-time release of products

• Lean manufacturing practices for reduced raw material, work-in-progress, and finished goods Inventories

• More robust product supply to the public

CONCLUSION

PAT offers the pharmaceutical industry a framework for revolutionizing its R&D and manufacturing businesses, producing value for themselves and ultimately, the patient and consumer. The use of process analytical technology can provide huge benefits to pharmaceutical industry by increasing product quality while delivering superior asset utilization and financial value.

PAT provides better knowledge of raw materials, by characterizing it both physically and chemically, understanding of manufacturing parameters all of which is having the impact on the finished product quality.

Combining together all of these results in a more robust process, better product, better process control and huge time saving which ultimately result in a good cost savings along with creation of a unique brand image for the organization.

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