

On-Line Monitoring and Process Analytical Technologies

Purpose

Process analytical technologies (PAT) are systems which provide continuous on-line monitoring of critical quality parameters and performance attributes of raw and in-process materials. Application of PATs to pharmaceutical manufacturing is an element of FDA's new risk-based approach to regulation described in "GMP's for the 21st Century," Reference (1).

In terms of technologies, implementation of PATs involves the application of analytical chemistry, sensors, feedback process control, and information management. On a more fundamental level, implementation of PATs requires a scientific understanding of the manufacturing process and the effects of the process on the physiochemical characteristics of the product. FDA believes that the enhanced process knowledge required to implement PATs will lead to better product quality, and industry proponents expect use of PATs will improve production efficiency and reduce manufacturing costs.

Recently, FDA has released draft guidance that discusses their expectations regarding the implementation of PAT. This guidance is contained in Reference (2). A fundamental element of FDA's thinking as described in the draft guideline is that use of PAT will drive more quality to be "built in" to the design of drug products.

This document provides a brief overview of the approach being used to examine and implement PATs in the industry and discusses the roles that MPR can play in this effort.

Summary of PAT Initiative

Historically, pharmaceutical production involves the manufacture of the finished product followed by off-line verification of product quality. An example, of the current approach to manufacturing is illustrated in Figure 1.

Manufacturing is performed in unit operations which are monitored and controlled using parameters that are straightforward to measure but that may provide only indirect indication of the product physical and chemical properties. In many cases, unit operations are controlled simply by time (e.g., a mixing operation may be specified to be performed at a certain speed and temperature for a certain period of time).

At specified points in the process, quality control chemists remove samples of drug, take samples to a lab for testing, and only look for the active ingredient or ingredients in a mixture of active

drugs and inactive ingredients. Out-of-specification results lead to an investigation which may or may not identify the root cause of the failure. Since process understanding is often limited to empirical observations of the effect of process parameters on product quality, the effectiveness of process controls is limited.

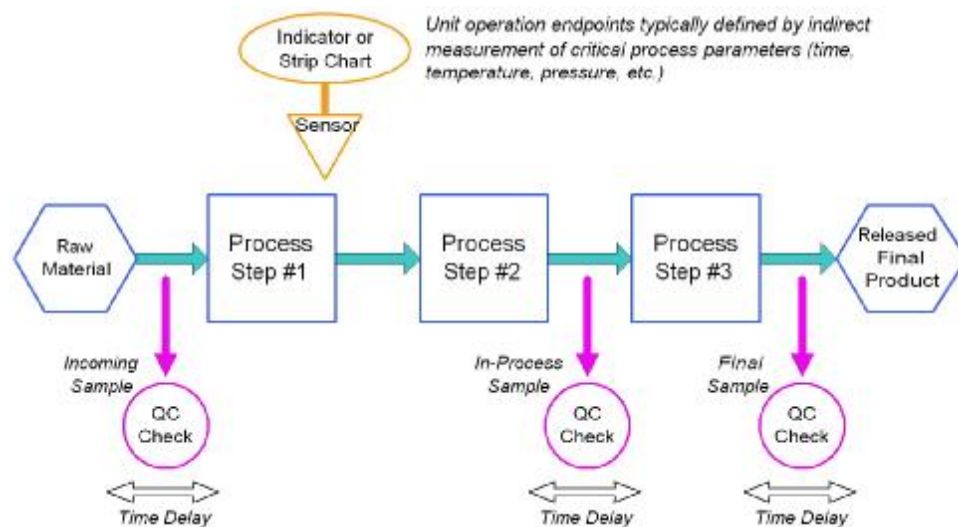


Figure 1. Traditional Manufacturing Approach

Although the current level of product quality is adequate for the intended use, the disadvantages with this approach are recurring manufacturing difficulties, the possibility of failed drug batches (often in excess of 10%), and the need for continuous process optimization. To remedy this sub-optimal condition, pharmaceutical companies are examining PATs for on-line process monitoring. The improved control gained from PAT is expected to provide benefits such as better batch-to-batch consistency, better quality due to fewer impurities, improved process understanding, faster response times, increased productivity, and lower costs.

The central objective of PAT is to generate product quality information in real-time. While process monitoring traditionally involves measuring temperature, pressure, flows, pH, and other physical parameters, PAT focuses on the use on on-line testing using infrared spectrometry, Raman spectrography, and other physiochemical techniques as a primary means of process monitoring.¹ A computer system retrieves and analyzes data in real-time to provide information on the properties of blends and other characteristics of the manufacturing process. Computer simulation of the process can be used with these data to predict product characteristics, allowing process parameters to be adjusted in order to achieve the optimal results. Monitoring these aspects of manufacturing is expected to ensure that the desired endpoint conditions such as uniformity, drying, and mixing can be pinpointed to a high degree of certainty. Figure 2 shows

¹ See the Appendix to this article for a brief description of several non-contact chemical analysis technologies.

one concept of how the PAT approach could be implemented in a manufacturing process in contrast to the approach illustrated in Figure 1.

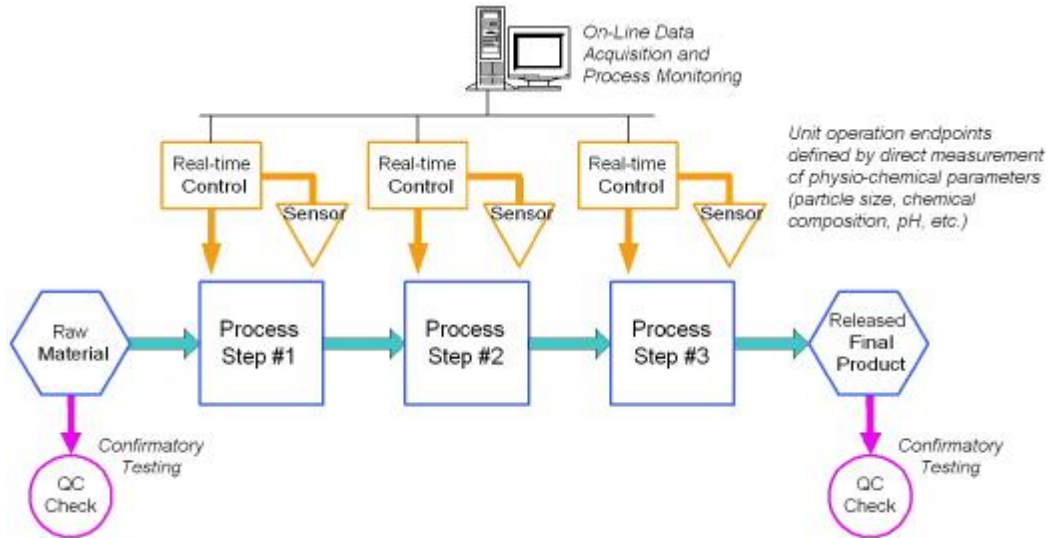


Figure 2. Manufacturing Approach with PAT

With increased knowledge of the manufacturing process and use of PATs for on-line monitoring, final product characteristics, such as dissolution rate, would be under such high control that the results could be accurately predicted well before the product is analyzed. In addition, because quality control using PAT is based on real-time electronic data rather than paper documentation, multiple individuals such as the manufacturing supervisor and the quality assurance manager could be simultaneously notified of any product quality problems.

In order to properly implement PAT, research on the correlation between end-test results and measured process parameters is needed so that the impact of the process, raw materials, and finished product variables is understood. Currently, many processes which are neither fully understood nor capable at commercial scales are transferred from the R&D to manufacturing. Lengthy and elaborate new product introduction exercises generate data but fall short of providing critical information which correlates end-test results with measured process parameters. Traditionally, 50% of production costs are locked in before Phase III begins, so many process inefficiencies are “institutionalized.” Therefore, the most significant advantages of PAT will be gained by moving toward complete process understanding, which is attained during process development. In turn, complete process understanding offers the opportunity for “quality by design” manufacturing methods.



Enabling Technologies

Design and implementation of a PAT system requires knowledge from several different fields of expertise, including pharmaceutical manufacturing processes, sensors and data acquisition, and analysis tools. This section briefly describes how these fields relate to PAT.

Pharmaceutical Process Development – Experience with pharmaceutical manufacturing processes is necessary to properly implement PAT. Often in existing pharmaceutical processes, parameters used to control the process are those that are easy to measure, but may not necessarily include those that are most representative of product quality. Actual product quality is usually a function of many interdependent variables. A critical part of a PAT initiative is to analyze the process to identify the true process critical parameters. This requires a greater investment in process development including more substantial experimentation and analysis of results. In order to truly understand the inter-relationships of the many variables that can affect a product, “design of experiments” techniques are needed for rigorous analysis of the process.

Sensors and Data Acquisition – Once the true process critical parameters have been identified, the appropriate sensor and data acquisition technologies are applied to measure and trend these parameters in real-time. PAT takes advantage of the latest advances in sensor technology, including chemometric methods such as Near Infrared (NIR) spectroscopy, and state-of-the-art computing.

Data Management and Analysis – A primary objective of PAT is to promote a deeper, first-principles understanding of the process to improve product yield and quality. One of the benefits of recent computer technology advances is the ability to collect, store, and analyze large amounts of data. Understanding and interpreting the data is in most cases crucial to process knowledge and control. Expertise in the state-of-the-art of tools for data retrieval, processing, and analysis can lead to cost-saving process improvements. High-performance trending, regression, and pattern recognition algorithms, as well as the integration of these tools into multifunction and user-friendly software and human-machine interfaces (HMIs) will enhance process knowledge.

MPR’s PAT Services

MPR possesses expertise that helps companies implement PAT-based systems in a variety of ways. Descriptions of a few of MPR’s services are below.

Process Development – MPR analyzes pharmaceutical manufacturing processes to determine whether the process could be improved using PAT. MPR identifies proven technologies that would enable the tracking and understanding of true process critical parameters, and ultimately the improvement of process efficiency.

Sensor Design, Development, and Testing – MPR has been closely involved with the design and implementation of a variety of highly specialized sensors for the pharmaceutical industry and other technology-based industries including national defense, nuclear power, and environmental remediation. These sensors include traditional sensors such as thermocouples and pressure transducers, and more advanced instruments such as acoustic measurement and fiber optic



sensors. MPR has designed and implemented many mission critical data acquisition systems, using either commercial or custom-designed hardware.

Process Modeling and Simulation – MPR has extensive experience with modeling physical systems using a first-principles approach. Combined with proven skill in both pharmaceutical processes and software development, MPR's can quickly identify and analyze the critical parameters of a process, and automate the analysis for real-time evaluation.

PAT Implementation – MPR helps pharmaceutical companies with existing processes and specific PAT needs to select sensors and data acquisition equipment. We develop protocols for trial evaluation of PAT systems and provide statistical analysis of the data collected. MPR also installs the hardware and develops software to analyze the data in real-time.

Root-Cause Investigation – If an existing process is generating poor yields, and conventional techniques are unable to identify or resolve the problem, MPR provides PAT solutions. MPR can examine the troubled process and identify PAT techniques that could provide improvements. As needed, MPR can perform multivariate data analyses and deliver recommendations for adjustment of the equipment or process parameters.

References

1. US Food and Drug Administration, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach," Concept Paper, August 21, 2002.
2. US Food and Drug Administration, "Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance," Draft, August 2003.

Appendix – Chemical Analysis Technologies

Currently, there are several methods for rapid, non-contact chemical analysis, and several of the more widely used technologies are summarized below. Each of the methods has its own advantages, disadvantages, and best application areas.

UV (Ultra-Violet) /visible spectrophotometry, the most commonly used traditional spectroscopy tool, recognizes a chemical by measuring the absorption spectrum after transmitting UV or visible light through a solution or a thin film. It requires sample preparation for the transmission measurement, which is a drawback for in-situ measurement.

FT-IR (Fourier Transform Infra-Red) spectroscopy uses either the transmitted or reflected infrared light spectrum generated by an IR source. When the frequency of the incident IR light matches the molecular vibration of a diatomic molecule (such as O-H, N-H, or C=O), absorption of the IR light is detected. The measured absorption frequencies from a sample can therefore be correlated with its chemical composition.

Like UV/VIS spectroscopy, a fluorescence spectrophotometer shines monochromatic light on a sample. While a UV/VIS spectrometer relies on absorption spectra after transmission of light through a sample, a fluorescence spectrophotometer picks up emission spectra that result from atomic excitation of the sample. For UV/VIS spectroscopy, a sample should be transparent, however for fluorescence spectroscopy, it does not have to be, making it more suitable for PAT applications.

The Raman effect is a fundamental process in which energy is exchanged between light and matter. When light impinges on a substance it can be scattered or absorbed. Most of the scattered light will have the same frequency as that of the incident light. However, a small fraction of the incident light can go into setting molecules in the material into vibration. The energy for this excitation comes from the incident light. The frequency change of this scattered light must equal the vibrational frequency of the excited molecules. This process of energy exchange between excited molecules and incident light is known as the Raman effect. The process of Raman scattering can be viewed as the transition of a molecule from its ground energy state to an excited vibrational state, accompanied by the simultaneous absorption of an incident photon and emission of a Raman scattered photon.

The Raman scattered light can be collected by a spectrometer and displayed as a “spectrum”, in which its intensity is displayed as a function of its frequency change. Since each molecular species has its own unique set of molecular vibrations, the Raman spectrum of a particular species will consist of a series of peaks or “bands.”



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