Process Analytical Technology and ASTM Committee E55

by D. Christopher Watts, Ph.D. Ali M. Afnan, Ph.D.
Ajaz S. Hussain, Ph.D.

Using traditional manufacturing methods, the pharmaceutical industry has, without question, provided quality drug products to the American public. However, there are opportunities for improvements in efficiency, process control, safety, and ultimately product quality, based on innovative approaches to manufacturing and quality assurance. Unfortunately, the pharmaceutical industry has been hesitant to innovate in the production arena. The most prominent reason cited for this hesitance centers on the regulatory environment surrounding the manufacture of pharmaceutical products. The U.S. Food and Drug Administration took a proactive approach to remove this hesitance from the industry, and established the Process Analytical Technology Initiative, a collaboration between the Center for Drug Evaluation and Research, the Office of Regulatory Affairs, and the Center for Veterinary Medicine.

The initiative was first publicly discussed at the FDA Science Board,(1) where leaders from industry, academia, and the agency highlighted the importance of innovation in pharmaceutical manufacturing and the associated benefits to public health, the FDA, and the pharmaceutical industry.

Recognizing that broad cooperation between the agency, industry, and academia would ultimately determine the success of the initiative, the FDA's Advisory Committee for Pharmaceutical Science established its PAT Subcommittee (2) with representation from all sectors. The PAT Subcommittee discussed all aspects of the initiative to assist in establishing an agency strategy for the PAT Initiative, including policy, teamwork, and training.

Discussions at various workshops and FDA Advisory Committee meetings identified several advantages of implementing the PAT framework. These benefits include:

- Reducing production cycle times by using on-, in-, and/or at-line measurements and controls;
- Reducing or preventing rejects, scrap, and reprocessing;
- Real-time release of products;
- Increasing automation to improve operator safety and reduce human errors;
- Facilitating continuous processing to improve efficiency and manage variability;
- Using small-scale equipment (to eliminate certain scale-up issues) and dedicated manufacturing facilities;
- Improving energy and material use; and
- Increasing production capacity.

Many similarities exist within the PAT Initiative, specifically: the risk-managed approach to regulation and innovation in pharmaceutical manufacturing, the facilitation and encouragement of new technology introduction and innovation in pharmaceutical manufacturing, and a team approach to review and inspection. Having this focus, the PAT Initiative was naturally enveloped in the much broader current good manufacturing practices initiative.(3) PAT is a system that uses process monitoring tools for designing, measuring, analyzing, controlling and integrating information on a manufacturing process to better understand processes and to continually improve product quality by reducing process output (product) variability.

Therefore, focusing on process monitoring and control, instead of end product testing, requires process control standards, practices and guides. The pharmaceutical industry's current quality control practices are based on validated processes and endproduct testing to specifications.

The FDA recognizes that the success of these efforts is strongly dependent on active participation and input from manufacturing experts from industry, academia, government, and consumer groups. In order to engage these groups to the fullest extent possible, the FDA participated in the development of ASTM Technical Committee E55 on Pharmaceutical Application of Process Analytical Technology.

Process Analytical Technology

The FDA defines PAT as a system for designing, analyzing, and controlling manufacturing through timely measurements (during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.(4) However, the unmistakable objective of PAT is to understand and control the manufacturing process, by integrating various efforts. Therefore, the term analytical in PAT must be viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. Simply, analytical is interpreted as "analytical thinking," not only analytical chemistry.

The focus on process understanding comes from the basic tenet of building — not testing — quality into products. Other industrial sectors (e.g., food and petrochemical) have recognized the futility of controlling product quality by testing the final product. A test of the final product should simply confirm the obvious, based on the direct measurement and control of critical quality attributes throughout the manufacturing process.

Considering any pharmaceutical unit operation in isolation from the entire manufacturing process would be ineffective in meeting the desired product quality attributes, as each procedure in the manufacturing process should be directed at meeting the needs of subsequent manufacturing operations, and ultimately, final product quality. For example, what attributes of the raw materials are critical to obtaining the desired granulation? What attributes of the granulation are critical to compression, or capsule filling? Most important, what attributes of the tablets, granules, raw materials, and the manufacturing process are critical to final product quality? As such, the focus of PAT is on the process, from development to production.

Additionally, understanding through innovation may not only come from strategies for measurement and control of traditional processes; novel approaches to pharmaceutical production itself may be developed as well.

PAT Framework

PAT has been described as a framework that focuses on understanding the manufacturing process. To that end, a process is considered well-understood when 1) all critical sources of variability are identified and explained; 2) variability is managed by the process; and 3) quality attributes of the granulation can be accurately and reliably predicted. Ultimately, the ability to accurately and reliably predict product quality attributes (via mathematical models) reflects a high degree of process understanding. This level of process understanding is inversely proportional to the risk of producing a poor quality product. Consequently, process understanding offers a risk-managed approach to regulatory scrutiny.

Obtaining an increased understanding of the manufacturing process requires a multidisciplinary approach, combining expertise and scientific principles from several fields, such as engineering, chemistry, and statistics. Similarly, successful implementation of the PAT framework requires cooperation across divisions within an organization, including the manufacturing, research and development, and quality units. Such cooperation within an organization is also necessary for regulation, hence, the FDA established a team approach to review and inspection for PAT.

PAT Tools and Their Application

There are a variety of tools available to facilitate increased understanding and provide the integrated systems approach to measuring, analyzing, optimizing, controlling, and modeling the granulation process. Many of these tools were developed and employed in other industrial sectors, but are beginning to find utility in the pharmaceutical industry. In its draft guidance for industry (*PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*), the FDA has categorized these tools as follows:

- Multivariate data acquisition and analysis tools;
- Modern process analyzers or process analytical chemistry tools;
- Process monitoring, control, and endpoints; and
- Continuous improvement and knowledge management.

In addition to the PAT tools, other scientific principles constituting the PAT framework were outlined by the agency in the draft guidance for industry. These principles include:

- Process understanding;
- Risk-based approach;
- Integrated systems approach; and
- Real time release.

In an effort to engage all stakeholders in delineating the PAT framework, ASTM Committee E55 was established. Committee E55 will address the standards necessary for the application and implementation of the PAT framework, including the specific tools and principles described above.

Committee E55 on Pharmaceutical Application of Process Analytical Technology

Working within ASTM affords the pharmaceutical industry the unique opportunity to learn from other industrial sectors that have established similar frameworks. PAT represents the FDA's vision for future pharmaceutical product development and manufacture. As pharmaceutical development and manufacturing evolves from an art form to one based on science and engineering, FDA will use the knowledge developed in PAT to establish product specifications and evaluate manufacturing processes. This is an opportunity to create improvements in the productivity of both the manufacturing and regulatory processes. FDA is partnering with other industry stakeholders in ASTM Committee E55 as the most effective venue for developing science-based consensus standards for "process quality," which is the focus of the PAT Initiative. Committee E55 addresses issues related to process control, design, and performance, as well as quality acceptance/assurance for the pharmaceutical manufacturing industry.

Collaboration with ASTM provides the pharmaceutical industry with opportunities to:

- Learn from other industrial sectors, such as petrochemicals, where the use of process analyzers, statistical principles, and risk management have been in practice for a number of years (and not "reinvent the wheel").
- Focus our efforts on "process" and bring a much-needed (pharmaceutical) engineering dimension.
- Work toward international consensus.
- Involve all stakeholders and multidisciplinary expertise (FDA does not have the resources to do this).

Conclusion

Implementing the PAT framework and having a greater understanding of the manufacturing process has obvious advantages to the pharmaceutical industry, regulators, and public health. Due to a change in the regulatory environment, pharmaceutical companies have been encouraged to innovate and employ the tools necessary to achieve an in-depth understanding of the manufacturing process. ASTM Committee

E55 will facilitate the implementation of the PAT framework through the active participation of industry, academia, and the FDA. This cooperation will be crucial as a drug quality system for the 21st century is developed. //

References

(1) FDA Science Board, Transcript, November 2001.
(2) Transcripts from the Advisory Committee for Pharmaceutical Science, Process Analytical Technology Subcommittee, February, June, and October 2002.
(3) In August of 2002, the FDA embarked on a major initiative to enhance the regulation of pharmaceutical manufacturing and product quality, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach." One goal of the initiative was to enhance the focus of the agency's cGMP requirements more squarely on potential risks to public health, by focusing regulatory attention and agency resources on those aspects of manufacturing that pose the greatest potential risk. The second goal was to ensure that the establishment and enforcement of pharmaceutical product quality standards does not impede innovation and the introduction of new manufacturing technologies in the pharmaceutical industry. Finally, the third goal was to enhance the consistency and predictability of FDA's centers and field components.
(4) *FDA Draft Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance*, September 2003.

About the authors

Ali M. Afnan, Ph.D., and **D. Christopher Watts, Ph.D.,** are both members of the PAT Team in the Office of Pharmaceutical Science at the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration. Their responsibilities include developing agency policy and training pertaining to PAT, coordinating submissions and discussions with the pharmaceutical industry, and collaborating in research ventures with industry and academia.

Ajaz Hussain, Ph.D., is deputy director, Office of Pharmaceutical Science in the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration. He also holds adjunct faculty appointments at Purdue University and the University of Michigan. Dr. Hussain has received several FDA- and CDER-level awards.