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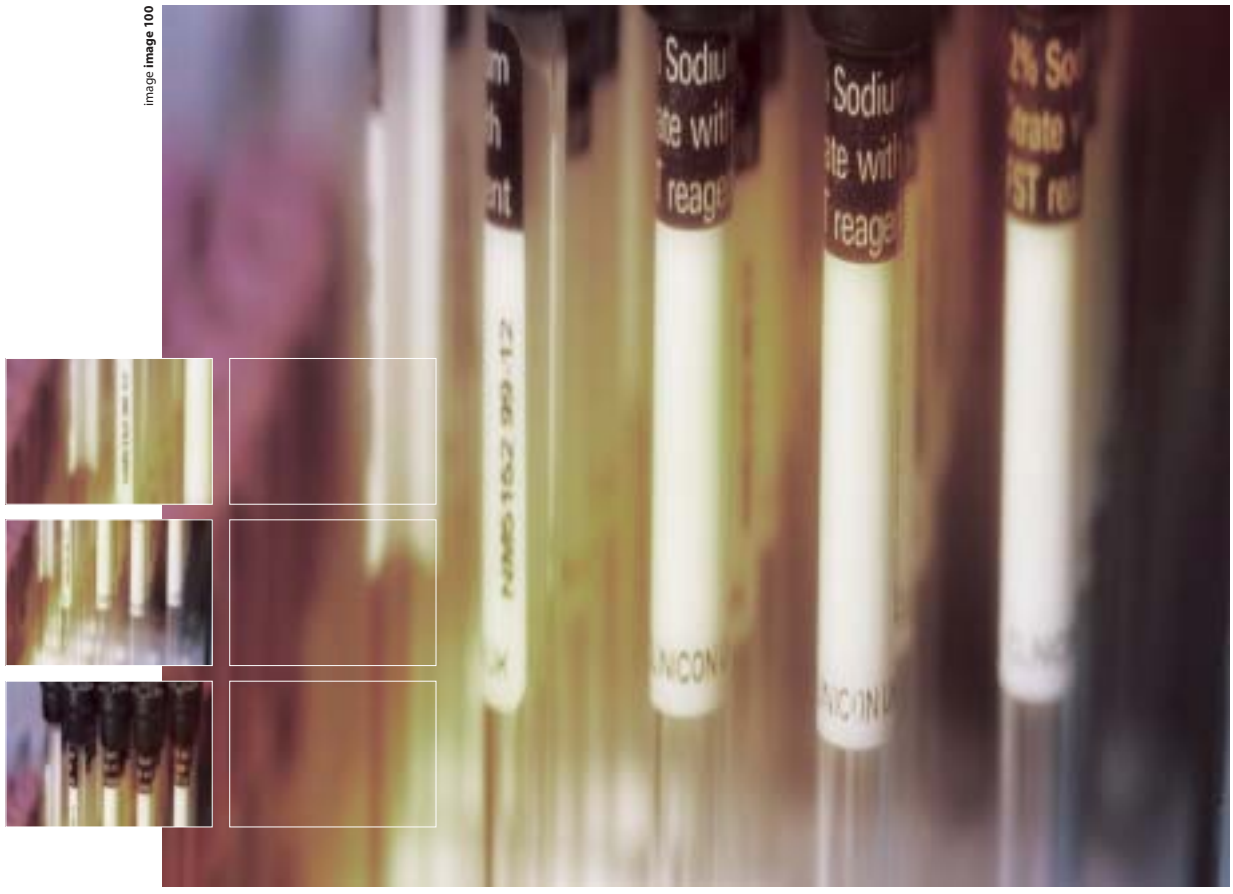
FDA's PAT Initiative



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FDA's **PAT Initiative**

FDA's recently released initiative has made process analytical technology (PAT) a hot topic in the life science industry. PAT describes the application of process analytical chemistry tools, feedback process control, information management tools, and product and process optimization strategies for the development and manufacture of pharmaceuticals. In this article, the author explores the impact PAT will have on the

Greg Clark
is a business manager at Honeywell Process Solutions' Life Science Competence Centre, Lovelace Road, Southern Industrial Area, Bracknell RG12 8WD, UK.
Tel. +44 1344 655 234
Fax +44 1344 655 454
greg.clark@honeywell.com

Under political pressure to lower the cost of drugs, the US Food and Drug Administration (FDA) has concluded that manufacturing costs are a major component of drug cost. It has realized that modern quality techniques are not being implemented in the pharmaceutical industry, as they have been in other industries, to achieve manufacturing efficiencies, and that the pharmaceutical industry is generally very hesitant to introduce new technologies and innovative systems. One reason often cited for this is regulatory uncertainty.

In response to these findings, FDA has changed its historic position of focussing on product purity and potency as its measure of quality, in favour of a regime spending more time on trying to address issues dealing with actual physical manufacturing processes. For example, what effects, if any, do small changes in the reactor vessel, blending, drying, pressing, coating or other manufacturing steps have on the final dosage form? To encourage this initiative and remove some of the previous disincentives, FDA is also streamlining the mechanism for adopting new technologies in pharmaceutical manufacturing.

What is the PAT initiative?

The process analytical technology (PAT) initiative was launched in August 2003 to promote the use of PAT to give a more thorough understanding of pharmaceutical manufacturing processes and, with this understanding, more predictable and efficient manufacturing. Although process analysers are potentially the vital tools, the PAT initiative is essentially about process understanding, predictability and efficiency. PAT should be thought of as a system for designing, analysing and controlling manufacturing through timely measurements, taken during the process or processes, of critical quality and performance attributes, and of raw and in-process materials

and processes, with the goal of ensuring final product quality. Associated benefits such as faster development of new products; shorter manufacturing cycle times; higher yields; reduced waste materials; and fewer product recalls should also be achieved by the greater understanding of the process gained by using this methodology.

Risk-based approach

Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk-Based Approach is an earlier initiative from FDA published in August 2002, which complements the PAT document. Together, they represent the current thinking of FDA and recognize the need to free industry from its current hesitant perspective. Its goals are to

- ensure that the most up-to-date concepts of risk management and quality systems approaches are incorporated into pharmaceutical manufacturing systems.
- encourage manufacturers to use the latest scientific advances and technologies.
- make sure review and inspection programmes operate in a co-ordinated and synergistic manner.
- ensure standards are applied consistently.
- promote innovation.
- encourage effective and efficient use of resources to address the most significant health risk.

Simply put, the regulatory oversight that FDA applies to a company will now be relative to the company's ability to manage risk. FDA itself now uses risk-based allocation of its resources; risk-based site selection for inspection; risk-based compliance programmes; and risk-based enforcement.

Some of the factors considered are the company's documented knowledge of the critical attributes of its product, the critical process parameters and the process capability. The manufacturing and process, the manufacturing and process control technologies used, and the quality system infrastructure of the company also play roles. Critical parts of the quality system are control of manufacturing processes and a strong and effective change control system that avoids surprises. FDA hopes that it will be able to work with the industry to achieve the following:

- Continuous improvement of product and process quality by employing effective feedback mechanisms.
- Use of methods and technologies that allow companies to better understand the factors critical to their product and process performance. This enables quality-by-design rather than quality-by-testing.
- Management of risk, by focussing on controlling critical process parameters, the assurance of which leads to real-time quality.
- Regulatory oversight appropriate to the risk.
- Safer plant and process operations through real-time monitoring and prevention of potentially dangerous process upsets.
- Assurance that processes and plant environments are in compliance with environmental regulations.
- An increase in process plant operability through timely adjustments in processes by using real-time data.

Integrated systems approach

This changed regulatory environment increasingly demands that the risks are mitigated by powerful control solutions that react to the data and implement the necessary feedback control; proactively enforce best practices, quality, and regulatory compliance while helping avoid the risks, costs and time delays of waste and errors; and most importantly, monitor all aspects of the system. As the electronic information emanating from PAT sensors becomes the initiating elements for changes in the process it becomes ever more important to ensure the reliability of that information. The need increases for asset management tools to continuously and automatically assess the health of not only the sensors directly associated with the process, but all other factors that could influence the results. In other words, close integration with, say, the environmental control system becomes very desirable if decisions are being made on the basis of calorimetry or any other temperature sensitive processes, while deviation handling capabilities are necessary to smoothly handle the inevitable hiccups. Furthermore, as PAT sensors supply more information on the process than ever before, it would be criminal not to use that information within the manufacturing execution system (MES) to improve cycle time, yield, schedule attainment, asset utilization, quality rate and throughput.

Close integration of automation architectures and manufacturing processes, along with control of the various stages of manufacture, MESs, environmental monitoring and security control becomes a necessity. Integrating the entire manufacturing life cycle of a product allows all information pertinent to the manufacture of that product to be available from one place. It simplifies security issues, and provides visibility and status at all stages of manufacture. What is needed are tightly integrated solutions that control and track every aspect of the product development life cycle, encompassing the five key elements of manufacturing: people, materials, facilities, equipment and documentation.

Both the PAT and risk-based guidance embrace an integrated systems approach to chemistry, manufacturing and controls (CMC) review and cGMP inspections. Companies will need to co-ordinate — particularly for PAT — development, manufacturing, environmental control, quality assurance (QA) and information/knowledge management functions in an integrated manner.

Consequently, upper management support for innovation is critical for successful implementation. The quantity and quality of information that will become available means that the traditional scientific method (used for hundreds of years) of control, namely:

- stating the problem
- forming the hypothesis
- observing and experimenting
- interpreting data (traditionally univariate)
- drawing conclusions related to complex processes and phenomena
- assuming the process is in control.

This must be superseded by a new scientific method (for problem solving using PAT) of

- measuring a process (any chemical phenomenon or process)
- analysing the data (multivariate analysis)
- iterating when necessary
- creating and testing (verifying) the model
- developing a more fundamental, multivariate understanding of complex processes
- making sufficient measurements to verify the process is in control
- using the verified information to automatically control the process.

Innovation

Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes that relate to product quality can provide a scientific risk-based approach to justify how real-time QA may be equivalent to, or better than, laboratory-based testing on collected samples.

To achieve this, manufacturing must employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management not just to continue as before, but to respond to the challenges of manufacturing new discoveries (for example, novel drugs and nanotechnology) and new ways of doing business (for example, individualized therapy and genetically tailored treatment).

Pharmaceutical manufacturing is going to continue to evolve with increased emphasis on science and engineering principles. Effective use of the integrated systems and use of process knowledge — throughout the life cycle of a product — can improve the efficiencies of both the manufacturing and regulatory processes.

Product quality and performance are ensured through the design of effective and efficient manufacturing processes. The tools necessary to optimize a PAT manufacturing process are available today. They include multivariate data acquisition and analysis tools; modern process analysers or process analytical chemistry tools; process and end-point monitoring and control tools; and continuous improvement and knowledge management tools.

These tools become more and more indispensable as recent innovations often provide measurements as complex signatures. Multivariate mathematical approaches become a necessity, while comprehensive statistical and risk analysis of the process is required to assess the reliability of the predictive mathematical relationship prior to implementation. Based on the estimated risk, a correlation function may need further support or justification. Mechanistic explanations of causal links between measurement target quality specifications, and sensor-based measurements can provide a useful process signature related to the underlying process steps or transformations. These signatures may also be useful for process monitoring, control, and end-point determination when these patterns or signatures relate to product and process quality.

Design and construction, and integration of the process equipment, the analyser, and their interface are critical to ensuring that collected data are relevant and representative of process and product attributes. The design of a process with a measurement system can allow real-time or near real-time (for example, on-, in- or at-line) monitoring of all critical attributes — process controls that provide adjustments (based on non-feedforward or feedback information) and can ensure control of all critical attributes. A process end-point need not be a fixed time, but can be the achievement of the desired material attributes.

Summary

Technologies that incorporate greater product and process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation. In a PAT framework, process validation can be enhanced and consist of continuous QA where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls and process end-point.

I believe that FDA's PAT initiative may soon have more impact on the pharmaceutical industry than any other recent FDA proposal, including 21 CFR Part 11 for electronic records and signatures. The PAT initiative promises to be a long-running show. Stay tuned. ■

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©October 2004 issue of:
Pharmaceutical Technology EUROPE
AN ADVANSTAR PUBLICATION

Article Reprint Number: 0630