Process Analytical Technology for Chromatography

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Abstract

A major United States Food and Drug Administration effort is devoted to process analytical technology (PAT), which is emerging as the likely "surprise" of the second half of the decade. PAT is an approach to monitoring, manufacturing, and other processes on a continuous rather than discrete basis. It carries the future promise of new methods of production. Building PAT into a chromatography system provides a significant cost and quality advantage to high volume multitest laboratories and provides a significant marketing advantage to the first suppliers able to implement such an approach.

Introduction

Effectively utilizing and managing modern biomedical laboratories requires, among other skill sets, a clear understanding of emerging United States Food and Drug Administration (FDA) agendas. Process analytical technology (PAT), a technique common in the petroleum and chemical industries, represents a new FDA initiative to be applied over the next 5 years to production, research and development, and clinical environments (1). This includes scientific equipment used in production quality control (QC) laboratories, research laboratories, and clinical testing and analytical laboratories fundamental to those environments. A PAT-monitored chromatography system would represent a significant improvement in QC in a cost containment context and may represent the next generation of FDA-encouraged self-regulation.

Surprises can be fun on certain occasions, but they represent reoccurring nightmares for regulatory professionals. New FDA directives that seemingly arrive with little warning and carry tight deadlines cause problems with budgets, result in confusion within laboratories and production facilities, and inversely affect the credibility of the quality assurance and regulatory affairs units.

For some companies, the announcement of 21 CFR Part 11 (2) represented an unwelcome surprise. Suppliers and users were suddenly faced with new requirements for signature verifications, archiving, and date stamping procedures that had not been anticipated in system design or purchase. Subsequent rescinding of Part 11 guidance and reissuing of clarifications and modifications increased confusion and resulted in further demands for advance warning.

But those who serve on or closely follow FDA committees had literally years of prior notice of Part 11. They knew months before the rescinding and reissuance of the confusions and reinterpretations that surrounded the electronic signature and record requirements. Not only had the surprise been "ruined," they had been given and had taken advantage of the opportunity to influence the new guidelines through a public and open input process.

The guidelines, regulations, and requirements of the U.S. FDA are never developed in isolation. They generally involve a lengthy process of discussion, draft announcement, comment, more discussion, issuance, and continued feedback. As a case in point, this paper describes the emerging regulations related to PAT—the new surprise regulation we will all be discussing in four to six years.

PAT

PAT was first discussed informally within the industry and the agency in early 2000. In 2003 a committee was formed to consider the possibilities. That committee has been issuing interim reports for the past 9 months (1). As the reports generate an additional discussion, a new draft guideline or regulation is likely to emerge, probably in 2006. It will be followed by a period of public comment prior to a final draft, presumably in 2006 or 2007. The resulting regulation will probably take effect sometime in 2008, with increasingly stringent enforcement or encouragement over the subsequent 3 years. By 2010 or sooner, an FDA investigator is likely to be asking pointed questions about your PAT capability.

PAT is an approach to monitoring, manufacturing, and other processes on a continuous rather than discrete basis. Traditionally, quality assurance (QA) monitors the safety and cleanliness of a production facility at all stages, but examines product only at end stage or predetermined interim stage. If the final sampling process indicates a contamination, dosage error, or other problem, the affected batch is destroyed or reprocessed. Then the cause is identified and corrected to avoid future problems. The procedure is not unlike taking a snapshot photograph of an event: a single moment is frozen in time for detailed observation and analysis.

PAT replaces the photograph with a streaming video. A process is monitored on a continuing basis (as well as at endpoint) to instantly detect and correct any problems. The final QA check is a valuable redundancy, but unlikely to detect any significant problems. The continuous monitoring provides a real quality advantage, but it is not the only source to a cost-effective, improved QC system.

Specifically, a PAT system has three key elements: First, as

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previously described, monitoring is conducted on a continuous, or frequent multiple discrete, basis. Second, that monitoring is cybernetic: deviations are automatically corrected without the need for intervention by a human supervisor.* And finally, the monitoring can be conducted remotely, allowing centralization of multiple monitoring functions.

PAT is not without precedent. The approach has been used by the chemical and petroleum industries for decades, largely because of safety concerns related to the volatility of potential interim byproducts. And the "zero defect" moment in automobile assembly, largely touted and occasionally implemented, is an attempt to introduce PAT in that environment: assembly line workers are empowered to monitor progress and halt and correct a problem rather than passing it on to a final quality inspector.

Chromatography Applications

Currently, PAT is configured in order to be valuable in a manufacturing application. However, the manufacturing process is largely dependent on the QC laboratory operations maintaining the product consistency and purity that PAT is attempting to monitor. In modern robotic and automated laboratories, the same continuous production approaches an originally developed manufacturing used in sequential and multiple discrete laboratory testing. There are significant chromatographic applications of continuous monitoring of a sample that will no doubt emerge in the not-too-distant future. Building PAT into a chromatography system will provide a significant cost and quality advantage to high volume multitest laboratories and will provide a significant marketing advantage to the first suppliers able to implement such an approach.

Imagine a laboratory (or production facility) utilizing a number of chromatographic systems, each with a PAT monitoring system that allows a QA professional, stationed at a central or remote location, to continuously monitor a self-correcting process. Perhaps that monitoring station would focus on global facilities for a single company or perhaps the biopharma industries will follow the pattern of the energy and chemical industries and contract with a few megacorporations to provide continuous monitoring of systems from many facilities owned by a number of laboratory and production companies around the world.

A single location, staffed by top-level chromatography experts, might monitor the majority of chromatography processes in operation at any given time, providing fee-based high expertise QC capability. The FDA could concentrate on the periodic visitation and investigation of that single facility, in effect moving regulation back a step to a single, wel-controlled, well-operated quality system. And, of course, because the costs of that quality system would be shared by a number of customer companies, a high level of investment in that monitoring would be cost effective.

That cost control, resulting in part through more efficient production processes and in part through the minimization of the necessity of final project rejects (or reprocessing) at the quality assurance final test point, is an important justification for exploring PAT. In a world in which financial issues have entered triage decisions, cost control has become tightly entangled with patient treatment and cure.

However, PAT brings other important advantages. Even the most rigorous military sampling of end product has a statistical chance of missing a problematic situation. In fact, the most dangerous of circumstances, human blood processing, requires regulation and a practice call for testing of all end products rather than a representative sample.† But the addition of monitoring during production as well as at end stage, even if redundant, can only enhance the likelihood of catching aberrant situations and increasing patient safety.

Perhaps most removed, but of great potential, PAT also carries the future promise of new methods of production. Continuous monitoring allows more controlled processes and a finer control of interim production steps. In vaccine production and chromatographic protein separation technologies, the continuous monitoring of PAT could potentially enhance the speed and quality of end product development.

Conclusion

Managing chromatographic systems requires currency in emerging FDA regulations. Currently, a major FDA effort is devoted to PAT. This is initially aimed at production but expanding over time to research and clinical environments.

Regulatory surprises actually provide ample advance warning: PAT is emerging as the likely "surprise" of the second half of the decade. Over the next 8 to 10 years PAT will evolve, develop, and focus to eventually become a major topic of regulatory concern. Once they are implemented, PAT systems offer advantages in cost control, quality, safety, and enhanced production capability.

Early recognition of PAT potential can help in budget planning, facility and system design, and market positioning (particularly for consulting groups and system suppliers). And an early involvement in the discussions and regulatory process can make it possible to help define and design future requirements.

References

1. U.S. FDA. "Steering Committee". In *Process Analytical Technology*. U.S. FDA, Washington, D.C. http://www.fda.gov/cder/OPS/PAT.htm, 2002 (April 12, 2005).
2. Part 21 of the Code of Federal Regulations , Electronic Records; Electronic Signatures (21 CFR Part 11). http://www.fda.gov/cder/guidance/5667fnl.pdf, 2003. (accessed April 12, 2005).
3. U.S. FDA. "Background". In *Process Analytical Technology*. U.S. FDA, Washington, D.C. http://www.fda.gov/cder/OPS/PAT.htm, 2002 (accessed April 12, 2005).
4. U.S. FDA. "Introduction". *Process Analytical Technology*. U.S. FDA, Washington, D.C. http://www.fda.gov/cder/OPS/PAT.htm, 2002 (accessed April 12, 2005).

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* Self-correcting feedback loops, as in the manner of a thermostat that self-adjusts temperature through a monitoring and controlling mechanism.

† Actually, several tests are conducted both prior to collection of blood and through (and simultaneous with) with processing procedure. As a final safety step, hospitals and physicians end users are instructed to conduct an additional blood typing test prior to use.