Pharma down PAT

An FDA initiative promoting continuous monitoring of the drug manufacturing pipeline appears to be gaining momentum.

BY CHARLES W. SCHMIDT

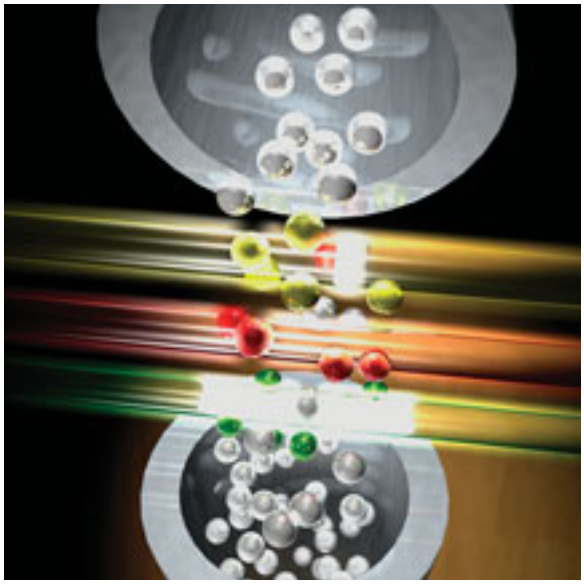
If the FDA's goals are realized, a controversial quality control paradigm based on a mode of operation referred to as process analytical technology, or PAT for short, may soon be widely adopted by U.S. pharmaceutical companies. PAT is designed to modernize quality control by shifting companies toward continuous product analysis using sophisticated instruments at every stage of the manufacturing process—to assess critical quality parameters and performance attributes of raw and in-process materials and to ensure acceptable end-product quality.

FDA officials say the new model will enable drug companies to improve efficiency and make safer products. "It allows them to gain a better understanding of their own processes," explains Ajaz Hussain, deputy director of the Office of Pharmaceutical Science in the FDA's Center for Drug Evaluation and Research (CDER) and the head of a broad-scale initiative to encourage adoption of the PAT paradigm among drug companies. "This helps to minimize the potential for drug shortages and product recalls."

A controversial paradigm

The FDA's PAT initiative—coordinated by a subcommittee to CDER's Advisory Committee on Pharmaceutical Sciences—represents an attempt by the agency to overcome its reputation. Many drug companies have been reluctant to explore the PAT model, fearing that discovery of "out-of-specification" products could invoke punitive measures from the FDA, says Mel Koch, director of the Center for Process Analytical Chemistry at the University of Washington in Seattle.

Some large drug companies, such as Pfizer, have incorporated PAT into their processes and are now working with the FDA to advance its initiative. Hesitation is strongest among small firms that don't want to absorb additional costs or potential regulatory delays in production, explains



Emil Ciurczak, an independent pharmaceutical industry consultant based in Goldens Bridge, NY. "Firms on a smaller profit margin don't want to use 2003 technology to analyze 1960s production methods," he says. "They are deathly afraid the government could use the information to hold up production."

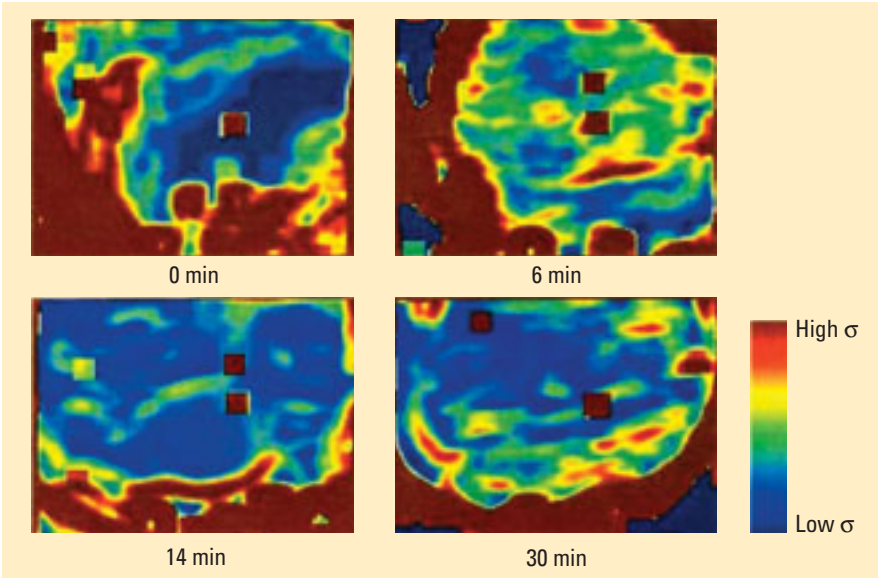
Most drug companies rely on a "testing to assure quality" approach to ensure conformity with FDA specifications. In a typical manufacturing sequence, batches of drugs are produced—a process that can take weeks or months—and then samples are removed and analyzed to confirm that dose ranges and other parameters are consistent with FDA requirements. CDER reviews these data in applications and during plant inspections. Experts concede the approach is cumbersome and inefficient. Out-of-specification products are often identified late in the cycle, leading to wasted materials and failed batches. This creates a "don't screw up" mind-set among manufacturers, who base production on elaborate approaches that often fail to provide critical information about basic operating procedures.

The PAT model, on the other hand, provides the opportunity to continuously monitor production with sophisticated instrumentation in real time. It relies on noninvasive analytical tools—including near-infrared (NIR) and Raman spectroscopy—that can be incorporated directly into the production cycle. "You can put NIR or Raman probes on a blender, a granulator, or some other processing device while the materials are being made," explains Jack Carroll, marketing and sales manager for the Olney, MD-based company Spectral Dimensions, Inc. In this fashion, he says, bulk chemical properties like sample composition, moisture content, homogeneity, degradation products, and particle sizes can be evaluated quickly and easily.

Spectroscopic analysis

Spectroscopic tools identify chemicals according to how they interact with light. NIR analyses are based on light absorption patterns, whereas Raman identifies chemicals according to how they scatter light. The resulting spectra are analyzed using computer software to provide information about molecular composition and concentration. The selection of appropriate instrumentation is process-dependent, says Patrick Treado, president of ChemIcon, Inc., a Pittsburgh, PA-based producer of chemical imaging instruments. For example, Raman is particularly effective with liquid samples. Conversely, solid samples are more appropriately analyzed with NIR.

A more recent spectroscopic advance for Raman and NIR is chemical imaging, a



Color time. Online NIR imaging, in this example used to monitor the effects of powder blending on active ingredient distribution over time, is an important tool for the PAT model (*J. Pharm. Sci.* **2001,** *90,* 1298–1307). (Image reprinted with permission. Copyright 2001 Wiley-Liss, Inc.)

technology that enables scientists to produce highly detailed "maps" of surface materials. The technology produces thousands of individual light spectra for discrete surface locations. Scientists use chemical imaging to hone in on a portion of a sample and thereby determine precisely how active ingredients are distributed. This is useful, explains Professor of Chemistry Laurence Nafie of Syracuse University, because it identifies potential clumping of ingredients. "You don't want the active ingredient concentrated on one side of a tablet," he says. "When the materials clump like that, they don't dissolve sufficiently and may not be absorbed well by the body."

An interesting observation is that PAT is already common among foreign pharmaceutical companies in addition to the overseas operations of U.S. companies. Pfizer, for example, has at least 30 PAT applications around the world, although few of them are located in the United States, according to a recent article by Jill Wechsler in the February 2002 issue of *Pharmaceutical Technology*. "Several companies complained that regulatory hurdles were preventing them from introducing the technology to U.S. manufacturing plants," Hussain admits. "We became concerned [at the FDA] that these firms were improving their process streams abroad but not here."

The current FDA initiative reflects the agency's desire to encourage, rather than hinder, the spread of the technology. Agency officials are busy holding meetings, conferring with stakeholders, and preparing guidance on specific PAT approaches, including NIR. These guidance documents are slated for release some time this year. Today, Hussain says, the regulatory burdens have dwindled. And the real challenge slowing the adoption of PAT, he emphasizes, lies with the companies themselves. "We've learned from [various] discussions that manufacturing departments are facing an uphill task when it comes to convincing their own regulatory affairs and R&D departments to move forward with PATs," he says. The reasons for executive-level reservations are varied: Some experts suggest drug company CEOs don't fully appreciate the value of manufacturing improvements, preferring to concentrate investments in advertising and R&D.

Furthermore, a pervasive fear of retroactive FDA action is a continuing concern. Noting that increased sampling will likely uncover "nonrandom trends" and increased out-of-specification units, Hussain has tried to reassure companies that "sound methodical approaches" will guide the FDA's remedial actions. Hussain said that these approaches would be based on statistical sampling to ensure that, for example, the dosage of active ingredient falls within an acceptable range of 75–125% of labeled strength. In addition, FDA officials have suggested companies that voluntarily undertake PAT will be protected by a "safe-harbor" clause from agency retribution. However, Hussain acknowledges that the legal definition of this clause for this particular application is still not clear. "We don't want to penalize companies for doing the right thing," he said. "We want companies to identify problems and improve their processes."

Transition to regulation

Ultimately, the movement toward PAT in the pharmaceutical industry appears to be gaining momentum. Treado says his company has already installed NIR and Raman spectroscopy for proprietary PAT applications in "five of the top six pharmaceutical houses" in the United States. The advent of FDA guidance on the matter also marks the first step toward what might be the inevitable regulatory framework that follows. FDA officials insist the current initiative represents an effort to promote PAT on a strictly voluntary basis. But stakeholders familiar with the agency see things differently. "Guidelines have a way of becoming law," says Carroll. "It's the FDA method for approving new schemes. Things tend to segue from guidance to regulation."

In the meantime, the FDA has undertaken a dramatic effort to train its own staff, which is important because companies investigating PAT claim that they often encounter limited agency experience with the technology. Expert consultants to the agency are being drawn from three sources: the Center for Process Analytical Chemistry at the University of Washington, the School of Chemical Engineering at the University of Tennessee, and the Purdue University School of Pharmacy. The goal, Hussain says, is to assemble a team of agency inspectors and reviewers to work with drug companies as they make the transition to the PAT paradigm. "We want to have a synergy between the inspectors and reviewers," he explains. "This way, we can be sure that a lack of technical knowledge at the FDA won't impede the industry process."

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