

Stand PAT

What does the accelerating adoption of PAT-based approaches to pharmaceutical manufacturing mean for the makers and users of spectroscopic systems?

John E. Carroll

PAT. You hear about it again and again, in the pharmaceutical and spectroscopic instrument worlds at least. What is it, why is it, and what does it mean for spectroscopists?

Above all else, PAT, or process analytical technology, is a health issue. As a major quality management initiative by FDA, PAT affects how the pharmaceutical industry will manufacture drugs in the future. PAT has other health implications, too. Look at the changing fortunes of the drug industry, consumer and legislative ire about prescription prices and the status of the spectroscopic instrument industry as bellwethers.

PAT doesn't imply conversion to on-line analytical sensing, although it can do so. Imagine a dash between "process" and "analytical" and the term becomes more nearly accurate. PAT is a push to bring the efficiency of pharmaceutical manufacturing in line with that of other specialty chemical production standards.

Make no mistake: the medicinal drug industry has an excellent track record of producing safe and effective drugs, but its manufacturing efficiency is embarrassingly poor. A September 2003 *Wall Street Journal* article carried this opening sentence: "The pharmaceutical industry has a little secret: its manufacturing efficiency lags behind that of potato chips and laundry detergent" (1). Numerical estimates of the industry's process efficiency range between 3 and 15%, a failing grade when compared with the semiconductor industry's 99+%. The comparison is apt: both industries are batch-process driven; both produce high-value products with attendant short lifetimes and high vulnerability to competition.

So why is big pharma, with its enviable pre-tax profit record, taking all this heat? Fifty years of steady growth and earnings contribute to the answer: big pharma has done well when it keeps its new-drug developmental pipeline full and obeys FDA's current Good Manufacturing Practice (cGMP) drug manufacturing rules. The picture is changing rapidly, however. And FDA is the catalyst for improving the health of the industry that it regulates.

Nearly four years ago, FDA's Center for Drug Evaluation Research began to marshal arguments from its own ranks, academia and big pharma-university consortia (2). The program led to a Guidance (3), issued in final form during September 2004, that offers the industry an opportunity to jump from rule-based to science-based chemical production. The 25-year-old GMP rules — part of the US Code of Federal Regulations — didn't die, but they can be set aside by scientific risk management.

Adoption of PAT manufacturing standards is not a sure thing: some large pharmaceutical companies have initiated aggressive

programs to use PAT as an integral part of their future business prospects. Most have a PAT development team in place. In some cases, however, there's a wary standoff between the host company's business and technical interests.

Drug manufacturers can continue to make existing drugs with no change in existing Master Manufacturing schemes. GMP laws are on the books, so industry members can continue to file New Drug Applications using conventional test-to-document methods. FDA, though, has trained a respectable number of inspectors as PAT review agents. Another group, using training programs jointly developed by the administration and the pharmaceutical industry, are well into their course completions.

So, the regulatory climate already has changed. What does the pharmaceutical industry have to gain, and how will members meet their goals? Time is the deadly enemy of pharmaceutical business health. A new drug entity can take 12 years to come to market. Patent protection starts with the early-on Investigational New Drug status of that chemical, so an \$800 million developmental clock starts ticking through those 12 years. If the drug fails along the way, a piece of that expenditure is lost. Assume that the new drug makes it to approval. Rushing it to market carries a risk of recall or worse — market withdrawal. A failure during the manufacturing cycle (assume that it is tested to GMP standards) could mean "rework, scrap or destroy" — a loss of market availability. The industry's overall portfolio is full of competing drugs for the same therapeutic need — look at all the cholesterol-lowering "statin" drugs. So, one drug-maker's lost time is another's market advantage.

Here's where PAT and spectroscopic instruments come into play. PAT has three tenets: Process Measurement, Process Analysis, and Process Optimization. Instead of "Test, File, and Forget" programs in manufacturing, PAT methods aim at understanding steps that are critical to product quality and then controlling them at each step of the way. PAT programs can reduce



IMAGE COURTESY OF EYEWIRE

or eliminate the expensive surprise factor at the end of the high-value-added batch manufacturing chain.

Which instruments are used in PAT programs? Well, that's the rub: PAT is science-based, so the user decides. Here's a maxim: "You cannot optimize what you do not understand" (4). Successful PAT programs almost always involve a period of intense over-testing, using several competing test instruments at the start. Results are evaluated statistically and the most appropriate instrument is selected for use. Because the drugs are batch-manufactured, each step in the process can use different instruments or sensors. Some PAT programs adopt "Swarm of Gnats" (5) sensors — a collection of "idiot savant" instruments that are deployable in multiples and that are instantly replaceable. Who decides? The user does; as long as the selection demonstrates good scientific foundation, the regulators will not challenge the choice.

Which types of spectrometers are appearing in PAT programs? In FDA's PAT Initiative Literature References, created in September 2003, near infrared

(NIR) appeared in 41% of the citations. Spectroscopic chemical imaging appeared at 6%, while NMR and Raman leveled at 3%. A year later, the picture is not much different: NIR continues to lead, but it has the advantage of being a "threaded" spectroscopic technology. There are in excess of 10,000 NIR instruments in pharmaceutical applications, the bulk involved in raw material identification. They also are used for preformulation, formulation, and scale-up work; tablet assessment; and in process-mode for blending, drying, and granulation monitoring. Hence, NIR is "threaded" throughout pharmaceutical manufacturing and has the advantage of familiarity.

And now for the "but." Five years of drug patent life involves 600–1200 manufacturing days per drug dosage form manufacturing site. For a drug that yields \$1 billion annually, that's \$830,000 per manufacturing day! And there are drugs on the market that yield in excess of \$10 billion a year. Pharmaceutical manufacturers that have embraced PAT principles are equating instrument cost expended with time and risk reduction. The result

is an upswing in purchases of fast, high-information-content instruments such as NIR chemical imaging systems, Raman chemical imagers and process-compatible NMR spectrometers. These tools carry a price tag 5–10 times greater than a benchtop NIR system but pharmaceutical manufacturing economics support the technology acquisitions.

There's one more "but." Remember those "Swarm of Gnat" sensors? They include "spectrometer on a chip" (6) NIR sensors. Thus, we are moving simultaneously to both bigger and smaller instruments for PAT. The new instruments also include non-spectroscopic inferential sensors such as thermal effusivity (7) and passive acoustic (8) devices. These devices offer multiple-point sensing at aggregate costs in multiples of two benchtop NIR units. They will, no doubt, be covered in far more detail in future technical articles.

The bottom line? PAT will be with us for a long time — after all, our current GMP methods have served the pharmaceutical industry for 25 years. And PAT has the potential of providing a healthy business environment for spectroscopic innovators.

References

1. New Prescription for Drug Makers: Update the Plants. Leila Aboud & Scott Henry, *Wall Street Journal*, September 12, 2003.
2. MIT Pharmaceutical Manufacturing Initiative (PHARMI), Massachusetts Institute of Technology, Cambridge, MA, G.K. Raju, and C.L. Cooney, directors; and Consortium for the Advancement of Manufacturing Pharmaceuticals, *ibid.*
3. *Innovation and Continuous Improvement in Pharmaceutical Manufacturing: Pharmaceutical cGMPs for the 21st Century*, USFDA, Rockville, MD.
4. Process Analytical Technology, Center for Professional Advancement, J.E. Carroll, director.
5. *Ibid.*
6. For example: Axsun Technologies (Billerica, MA).
7. For example: Mathis Instruments (Fredericton, NB Canada).
8. For example: Process Analysis & Automation Ltd. (U.K.). ■

John E. Carroll is president of Carroll Ventures, Inc. and managing partner of Cadrai Technology Group (Bel Air, MD). E-mail: info@cadraigroup.com.