GEA

CONTINUOUS MODE In drug tablet production, in-line probes monitor drying and blending and on-line laser diffraction measures particle size. Physical testing of the final product is combined with near-infrared chemical analysis.

REAL-TIME MONITORING

Although **PROCESS ANALYTICAL TECHNOLOGY** is finding a home in drug manufacturing, progress is slow

ANN M. THAYER, C&EN HOUSTON

RAW MATERIALS get verified by using handheld Raman scanners. Reactions are monitored in situ with probes attached to optical spectrometers. Near-infrared, Raman, and reflectance devices track crystallization, drying, and particle formation as they happen. And finished tablets are examined chemically and physically as they tumble off the line.

Process analytical technology (PAT) appears in all stages of pharmaceutical production. But drug companies have been slow to achieve the vision laid out for them by the Food & Drug Administration 10 years ago: complete, closed-loop use of in situ analytics in process design, monitoring, and control.

The vision is that through process understanding, control strategies, and measurement of critical attributes of materials and processes, drug manufacturing will improve and final product quality can be assured. It's a practice followed already in industries such as food and chemicals. Pharma, however, continues to look for the right technologies to make the right measurements.

Analytical instrument makers are only too happy to help, but determining the right measurements won't be easy. "Industry remains challenged by understanding what attributes are most important," says Tim Freeman, former head of the PAT focus group within the American Association of Pharmaceutical Scientists. On top of that, he says, the challenge for PAT is to develop technologies relevant to the parameters that must be measured.

"What is missing is a fundamental understanding, a number of technologies at- or on-line, and the closed-loop ability to control the process," Freeman says.

PAT IN PRACTICE

Both internal and external impediments to PAT implementation can arise, according to the International Consortium for Innovation & Quality in Pharmaceutical Development (IQ Consortium), a group representing 35 pharmaceutical firms that supports greater use of PAT.

Internal corporate hurdles around PAT include uncertain returns on investment, staff capabilities, differences between R&D and manufacturing, and integration into quality systems. Incompatibilities among

many types of hardware and software from different vendors and differing regulatory expectations are some external challenges.

In light of the impediments, industry's need to attain FDA's PAT vision "is heartily discussed and debated," the IQ Consortium reported in a recent review article (*Org. Process Res. Dev*. 2014, DOI: 10.1021/op400358b). Nevertheless, companies continue to identify and implement controls, "irrespective of the type or location of the analytics and controls or whether additional cost benefits could be achieved using in situ analytics and real-time control."

When it works, PAT can enhance quality, safety, and efficiency in drug manufacturing, according to the IQ Consortium. For example, faster cycle times are possible by avoiding the need to scrap or reprocess products. Automation can reduce errors, allow for more frequent testing, and eliminate the handling of hazardous samples. Better control improves material and energy use.

Ultimately, regulators expect that less process variability may allow for the real-time release of final products of predefined quality. Drug manufacturers are also eager to enjoy the more flexible regulatory oversight that FDA has suggested will accrue to firms demonstrating better process understanding, Freeman explains.

As a result, collaboration among pharmaceutical, equipment, software, and instrumentation companies is growing. "All are part of the picture, and it has to be a complementary approach," adds Freeman, who is managing director of Freeman Technology, a U.K.-based firm that develops instruments for characterizing powders.

Such partnerships are key to success, agrees Dave Nadig, vice president for analytical development at Boston-based Vertex Pharmaceuticals, which has been developing a PAT-enabled continuous production process. "But taking the leap to modern manufacturing methods takes commitment and work from regulators and manufacturers together," he says.

PAT IN PROCESS

Companies often first try out PAT in R&D, where scientists use an array of analytical methods to reveal reaction details, according to the IQ Consortium. This information may be used to construct mechanistic and chemometric models of their processes. Whether qualitative or quantitative, these models are most useful when, coupled with in-process measurements, they can be used to adjust process outcomes.

The analytical data also shape process design, assist scale-up, and help direct possible control strategies. As manufacturing processes move from the lab to the production plant, process developers decide which steps are amenable to PAT and what the costs and benefits of using it are. Choosing and installing these tools often results in increased collaboration between R&D and manufacturing.

As the work progresses, and a process is better understood, a development team selects appropriate PAT systems for data collection and monitoring during production. Companies that have incorporated PAT methods in this way are using them in batch and continuous processes for manufacturing active ingredients and finished dosages. In the full vision of PAT, the tools would not only track a process but also feed information back into it for real-time decision-making and adjustment.

No single analytical tool will work for all applications, the IQ Consortium warns. The appropriate choice will be determined by the chemistry, availability of the technique in the lab or plant, configuration of the process equipment, personnel skill levels, and regulatory acceptability.

characterize what is happening. "It really needs to be a 'yes/no—do I proceed or do I stop?' type of application," he says.

Near-infrared (near-IR) spectroscopy has made the biggest inroads on the pharmaceutical plant floor. In 2013, FDA reported that near-IR constitutes the majority of PAT submissions it sees and has approved. This year, the European Medicines Agency finalized its guidelines on near-IR spectroscopy use and data requirements. The technique is used most often for material identification, followed by the monitoring of drying, content uniformity, and blending.

As a proven technology, near-IR is used by all the large drug companies from R&D through final product manufacturing, according to Yan Wang, regional applications manager for Bruker's optical spectroscopy business. Generic drug makers are adopting it as well. After an up-front investment to install instruments and develop methods, most companies "see benefits in the long run and a payback maybe within a year or two," he says.

Aided by FDA prodding and a growing realization of financial benefits, sales in the sector are rising. In 2013, pharmaceutical industry spending on PAT instrumentation reached $305 million, according to the Wellesley, Mass.-based market analysis firm BCC Research. This market is expected to grow nearly 7% per year to reach $450 million by 2019.

Pharma is part of a larger PAT market for process instruments and controls that industries such as food, chemicals, water treatment, and power generation have used for decades. Like the broader market, the pharma sector is served by large software and control system providers; major instrumentation firms, such as Bruker, Thermo Fisher Scientific, and Mettler Toledo; and niche players with specialized fit-for-purpose detectors and probes.

"Large pharma companies realize that what they do in the lab is very difficult to mimic on the production side."

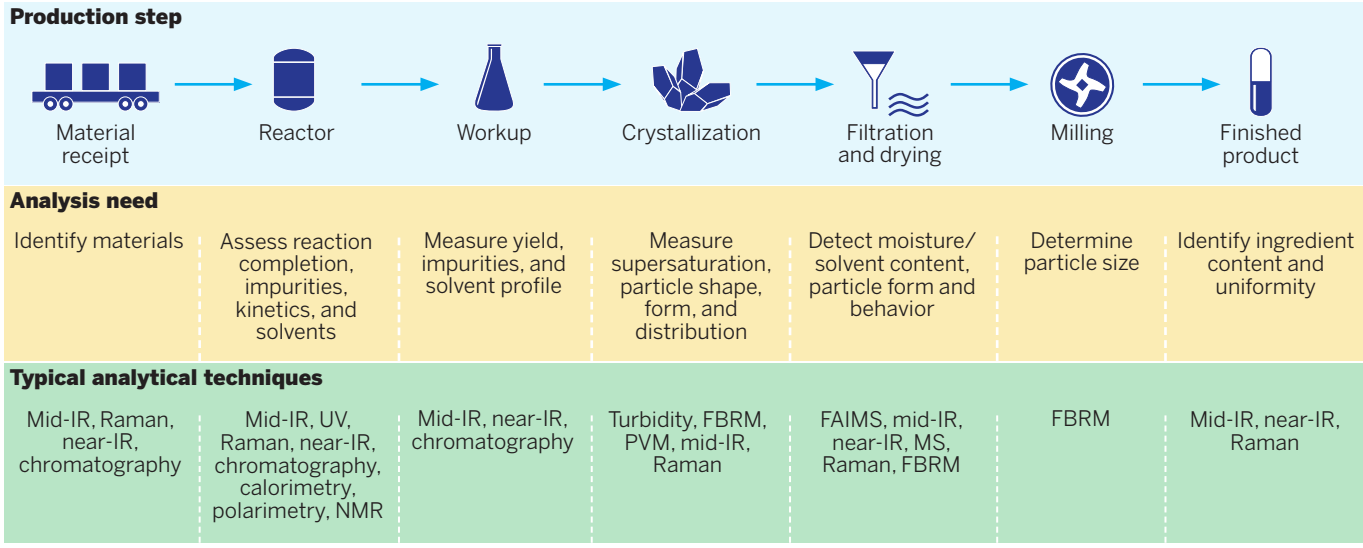
"Large pharma companies realize that what they do in the lab is very difficult to mimic on the production side," says Bob Galvin, vice president for biopharma with Bruker's mass spectrometry business. Whereas people in development see the benefit of having the same analytical technologies downstream in manufacturing, at the moment, manufacturing folks don't see the need to have the same level of complexity, he says.

Instead, they opt for methods that are fast, simple, and reliable, Galvin adds. Plant employees probably won't have the skills or time to do the in-depth analysis that occurs upstream in the development labs, where scientists can work to fully understand and

AT-, IN-, OR ON-LINE

PAT systems generally operate at least at-line—or near to a process—but they work better when the detection method is in actual contact with a reaction or material.

PROCESS FLOW Steps in drug manufacturing call for different analyses and analytical technologies.



Key:
FAIMS = Field asymmetric ion mobility spectrometry
FBRM = Focused beam reflectance measurement
MS = Mass spectrometry
NMR = Nuclear magnetic resonance
PVM = Particle vision measurement
UV = Ultraviolet

SOURCE: Adapted from the International Consortium for Innovation & Quality in Pharmaceutical Development in *Org. Process Res. Dev.* 2014, DOI: 10.1021/op400358b

Operating directly in-line, or diverting a sample on-line, can avoid sample handling and allow measurement of transient species. Though near-IR and other optical spectroscopies interface easily via in-line probes, practical issues arise around probe fouling and reliable testing, especially of heterogeneous mixtures found in drug production.

Looking to integrate PAT into its equipment for processing solids, Brussels-based GEA Pharma Systems surveyed existing probe and instrument products. "In the end, we weren't very happy with what existed on the market," GEA Senior Process Technologist Tomas Vermeire recalls. "We had quite some trouble getting things working and doing representative measurements."

Instead of the standard lab tools available, he says, "we wanted a reliable and robust process interface allowing us to do measurements in all our machinery." So GEA worked with Germany's J&M Analytik to design a fiber-optic interface, called the Lighthouse Probe, that can link to several different spectroscopic techniques simultaneously. In manual or fully automated mode, the probe's main feature is that it can be cleaned and calibrated in-process.

GEA used its in-line probe when it worked with other suppliers to build a continuous tablet manufacturing system for the drug company Janssen. The system also uses GEA's powder handling and tablet compression equipment, along with Siemens software. And it incorporates Bruker's automated Tandem near-IR testing system to determine ingredient levels in tablets and measure physical properties.

Vertex has developed a similar continuous tableting system with GEA that uses 10 PAT components, including near-IR, Raman, light scattering for particle sizing, and measurements of tablet hardness and weight. The components monitor and confirm the quality of every operation, from the blending of drug substance and excipients through granulation, drying, tableting, and coating operations.

PAT allows the continual monitoring of manufacturing conditions to ensure that the process is in control and quality is maintained. "Alternatively, PAT allows the removal of potential nonconforming material immediately after its detection," Vertex's Nadig explains.

The system meets the definition of real-time release testing, because quality control (QC) testing is complete when manufacturing is over. "PAT allows Vertex to use the upstream QC data to assess the final product's quality more efficiently than the use of end-product QC lab testing," Nadig says.

The move from a stepwise batch to continuous process has accelerated decision-making. "Rather than stopping for days or weeks between unit operations, with PAT, we immediately move material to the next unit operation," Nadig says. It has taken a balance of technology and human oversight "to get it right and get it fast."

PAT-enabled systems can generate real-time measurements and quality assurance by detecting minor changes relative to predetermined intermediate- and finished-product attributes. But more difficult is to use the gathered data for feedback control, GEA's Vermeire explains.

"Analyzing the data, seeing how far you are off-target is easy. Automatically making the adjustments that you would actually need is harder to achieve," he says. The problem comes from the complexity of the processes; optimal performance can depend on a variety of interrelated parameters, and adjusting one can lead to other—sometimes unwanted—changes.

Chemometric modeling and multivariate data analysis are PAT tools that may help close the loop. Process data need to be analyzed in real time and compared to reference models so that operators understand what is occurring in a process and keep it under control. But understanding of the process must be crystal clear before observed variations can be related to real process adjustments that need to be made.

BENCH TO PLANT

Ideally, manufacturers want to juggle as few analytical techniques as possible. Sur-

rogate methods that correlate to more advanced techniques are substituted when they can be implemented more readily in a plant setting. Oftentimes, measurements as simple as time, pressure, and temperature are used.

Some spectroscopies, however, may simply provide better analytical information than others. In such cases, it may be possible to adapt the technology for manufacturing use. Beyond the first step of interfacing to a process, modifications can include eliminating the need for involved sample preparation and changing performance specifications.

For example, process mass spectrometry has been used for decades to monitor industrial processes, including fermentation, says Peter Traynor, Thermo Fisher Scientific's MS sales leader for environmental and process monitoring. The company's process MS systems have lower mass ranges and resolution than their lab counterparts but are high precision, stable, and rugged. They only measure gases, however.

Process MS was quickly adopted for biological processes such as fermentation because, as an indirect, on-line technique, it is minimally invasive and avoids contamination. "You monitor the gas composition going into the reactor and the gas composition coming out," Traynor says. "Calculations about the respiration metrics tell an awful lot about how a batch is progressing."

The same approach can be used to assess solvent levels during the preformulation drying of drug substances, without testing the material directly as one would via a probe. "We can monitor the solvents coming off the material from atmospheric pressure all the way down to a few millibar," Traynor says.

Making the move from lab to plant should be similar for nuclear magnetic resonance spectroscopy, which typically involves expensive and high-maintenance machines run by trained operators. Although widely used during process development, NMR hasn't made significant inroads to the manufacturing floor, says Kimberly L. Colson, a business development manager in Bruker's NMR division.

Among the best methods for compound identification and quantitation, NMR is particularly good for monitoring reactions and lends itself to tracking products, impurities, and kinetics. It can even be used in flow mode. Colson anticipates that initial PAT applications will be at-line and eventually move in-line. And although the technology now is used mostly for data gathering, she believes it will also be used to make "real-time process control very possible."

Other NMR manufacturers are also moving in this direction. In late 2012, Thermo Fisher acquired Colorado-based PicoSpin with the idea of extending its portable, bench-scale spectrometers, designed for the academic market, into the process area. These more affordable low-magnetic-field and noncryogenic systems have many of the features needed for a PAT system.

The newest PicoSpin 80-MHz system can be used at-line, with reaction samples injected directly into the spectrometer, says Mark Dixon, NMR product marketing manager at Thermo Fisher. "We are working on a reaction monitoring accessory that we hope to launch by first-quarter 2015."

For more direct monitoring, an on-line version will likely use a stop-flow mechanism and control software to divert and test samples, he says. Thermo Fisher also plans to offer customized chemometric software services, as well as the operating procedures and validation protocols pharma customers will need to comply with drug manufacturing regulations.

The business drivers for new and expanded PAT methods are emerging. "FDA is definitely asking for the right technology for the right application, and they do not tolerate anymore just doing whatever analytical technique is handy to prove the purity of a material," Colson says.

But the drug industry's late embrace of PAT arises in large part from its historical reluctance to adopt new technologies and change validated manufacturing processes. "Shutting down or changing their processes is sometimes unsurmountable," Colson says.

Expectations are that PAT will more easily gain traction in processes developed for new drugs, especially with the trend toward continuous manufacturing of both active ingredients and final products. Although it's happening slowly, FDA's vision of PAT-enabled drug manufacturing may yet be realized. ■

THE RIGHT FIT

Requirements for analytical technology differ by process stage

	PROCESS DEVELOPMENT	PRODUCT MANUFACTURING
Purpose	Process understanding	Control, trend analysis
Desired technology	Multicomponent analyzers	Targeted analyzers
Data requirements	Multivariate	Univariate (desired) or multivariate
Support needs	High level, continuous	Minimal, automated, robust
Quality management	Development practices	Current Good Manufacturing Practices
Expertise	Method design, development	Operation, maintenance

SOURCE: International Consortium for Innovation & Quality in Pharmaceutical Development in *Org. Process Res. Dev.* 2014, DOI: 10.1021/op400358b