Cynthia A. Challener

PAT for Continuous API Manufacturing Progresses

Advances in process analytical technology have been achieved, but significant challenges remain.

Continuous API manufacturing has the potential to provide tremendous benefits to the pharmaceutical industry—smaller plant and environmental footprints, reduced costs, and improved processes with more consistent quality. Extensive process and product knowledge and the ability to control process conditions in real time are necessary for achieving these goals. Effective process analytical technology (PAT) for online monitoring during research, development, and commercial manufacturing is therefore essential. While notable advances have been made, there are numerous challenges yet to be overcome. Manufacturers, instrument suppliers, and data analysis and process control system vendors are working collaboratively to design effective solutions.

Many choices

PAT can be used for many different objectives, including reaction/process characterization, process development, and long-term, robust installations. At Eli Lilly, PAT implementation is used to pursue all three, according to Todd Maloney, principal research scientist. During process development, adds Nuno Matos, head of continuous manufacturing within R&D with Hovione, the main driving force for using PAT is to enhance knowledge gathering. Therefore, more versatile, complex technologies with high dynamic ranges are used.

Spectroscopic methods are most widely used because they are non-invasive and non-destructive. Chromatographic separation combined with various detection techniques is increasingly used due to the additional specificity, higher sensitivity, and resolution it offers and with the advent of faster technologies such as ultra-performance liquid chromatography (UPLC) or ultra-high pressure LC (UHPLC), according to Ernie Hillier, principal systems manager, Waters Corporation.

Early efforts typically emphasize elucidation of the chemical mechanism along with gaining kinetic information relevant to the reaction. Eli Lilly heavily leverages flow–nuclear magnetic resonance (NMR) along with other *in-situ* spectroscopic measurements including Fourier transform infrared spectroscopy (FTIR) and Raman spectroscopy. "These data-rich experiments drive process development by providing critical information at an early stage and also serve as inputs to reaction modeling efforts," says Gordon Lambertus, senior research scientist with Eli Lilly. At Hovione, the most widely use technologies also include mid-IR and Raman spectroscopy, in particular for reaction and crystallization monitoring, according to Matos. Chemometrics are applied to collected spectra to maximize the information that can be extracted.

As chemical mechanisms become understood, more emphasis is placed on process development, with efforts focused on monitoring reaction conversion and tracking process-related impurities to optimize reactor platforms and reaction conditions. "Process monitoring attributes of interest at this stage are typically focused on supporting the overarching control strategy for the process, commonly including removal of many low level process impurities," Maloney observes. He adds that online chromatography is the single most important platform technology used to support process development because no other analytical tool offers the specificity and sensitivity required for analysis of these low-level species. Eli Lilly largely employs online high performance liquid chromatography–ultraviolet (HPLC–UV) detection, but also uses HPLC–mass spectrometry (MS), gas chromatography–thermal conductivity detection (GC–TCD), and GC–flame ionization detection (GC–FID) when appropriate.

Spectroscopic tools such as FTIR, Raman, near infrared (NIR), UV, refractive index (RI), and fluorescence are strategically implemented for specific applications, as are simple sensors that cover additional analytical space and often offer more robustness over the course of a long-term installation, according to Lambertus. These sensors include some spectroscopic measurements (UV, RI, fluorescence), monitoring of specific chemical entities (e.g., pH, dissolved oxygen), and physical property measurements (e.g., turbidity, viscosity, conductivity). "A key

Cynthia A. Challener is a contributing editor to *Pharmaceutical Technology*.

point is that there is no single solution, so we have built quite an extensive toolbox that includes a wide range of analytical technologies," asserts Lambertus.

Valuable information

Process dynamics in continuous manufacturing should be well understood, namely how process parameter variability will affect the quality attributes of interest or how predetermined changes in process parameters and material attributes will influence the outcome of the continuous step, according to Matos. "Capturing this information requires analytical technologies that can output in real-time the data of interest (either directly or via prediction). As a result, experiments for determining residence time distribution, building kinetic models, or executing design of experiment approaches will be data- and information-richer," he explains.

The more data that can be collected from a single experiment, the more efficient the process development model becomes, agrees Lambertus. The two most widely used PAT tools in his department are flow-NMR and online HPLC because of the amount of information they provide.

"Flow–NMR provides information relevant to understanding chemical reaction mechanisms through elucidation of transient species or monitoring reactive intermediate species, readily generating kinetic information and providing valuable inputs to chemical reaction models that help in optimization," Lambertus notes. It also allows for access to reactions that could not be run in static NMR tubes (e.g., heterogeneous reactions, high pressure reactions).

Online HPLC is used in R&D and manufacturing at Eli Lilly to support various control strategy elements. Online measurements are required because there are few isolated intermediates in most continuous synthetic routes that offer traditional control points where measurements can be made, according to Lambertus. He adds that HPLC is the preferred measurement technique because many of the control elements of a process are related to species present in the solution matrix at low levels. "No other analytical technique is capable of detecting and quantifying at the low levels necessary to show that the process is performing as expected with respect to those impurities (e.g., residual starting material, genotoxic impurities, identified impurities with poor rejection efficiency)," Lambertus says.

Technology gaps remain

"During the past decade, the PAT user community has been seeing important technological developments; equipment manufacturers are not only improving established technologies but also adapting complex technologies for real-time monitoring," Matos asserts. There are still unmet analytical needs in the continuous API manufacturing space, however.

Matos notes that NMR spectroscopy is a good example of an analytical technology that is seeing important developments for going from bench to process applications, with manufacturers racing to make these units smaller while not losing too much resolution. Online UHPLC is a reality, but even runs of a few minutes can hinder real-time monitoring, and interfacing with process equipment requires complex automated sampling devices, so this technology is currently more often used in an at-line fashion.

The separations piece is still needed, though, according to Hillier, and UPLC provides the high sensitivity and resolution required to gain greater process knowledge. Introducing new technologies is always challenging, he adds. "It is difficult to generate interest when there are existing technologies that are well understood, respected, and do an adequate job. From time to time, we've had to contend with perceptions that liquid chromatography is a slow process that requires extensive technical skill to perform," Hillier comments.

For Eli Lilly, online metals analysis remains a significant need. "Integrated continuous processes, by nature, eliminate many of the intermediate isolation points of traditional pharmaceutical manufacturing processes. Without these isolation points, inorganic species (salts and metals) can potentially be carried through many subsequent unit operations. Continuous extractive workups are incorporated as rejection points for these types of materials, and currently we use at-line instrumentation based on x-ray fluorescence (XRF) technology to do

Contaminated water and trashed data lead to warning letter

In a warning letter dated March 2, 2017, FDA cited Badrivishal Chemicals & Pharmaceuticals with current good manufacturing practice (CGMP) violations found at the company's Maharashtra, India facility. The violations, which include quality and data integrity deficiencies, were observed during an FDA inspection conducted Aug. 16–19, 2016.

Quality CGMP violations included an inadequately monitored and controlled water purification system. Source water from a nearby river was not tested and was kept in a storage tank with a hole open to the environment—violations that caused the potential for water contamination and, therefore, product contamination. Procedures for sanitizing the water system were not followed, nor had the company completed a performance qualification of the water system. FDA reported that the company was aware the water system had an excessive amount of total aerobic microbial counts, failed to investigate the deviations, and provided an inadequate response to investigators' findings, the letter states.

Investigators also found original laboratory and production records in trash bags behind the facility containing data that did not match official records; the quality unit did not investigate the discrepancies. FDA investigators later found that the trash bags containing the documents had been removed; preventing further FDA examination of the documents, the agency stated.

In addition, the company also failed to ensure that contract testing laboratories were qualified. When asked to provide method verifications, the company provided draft protocols and did not specify which contract testing laboratory performed the verification experiments.

FDA placed the company on Import Alert 66-40 on Dec. 19, 2016.

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analysis of metals around these workup unit operations. There is a strong desire to have instrumentation for online, quantitative metals analysis available to support continuous process development," Lambertus explains. He would also like to see more traditional oxygen and pH sensors that have the chemical compatibility and robustness required for use in aqueous/organic mixtures or neat organic solvents.

Nanoparticles—with a median particle size typically in the range of 100–600 nm—also present online analytical challenges, according to Matos. "Applications involving nanoparticles are growing in number and the manufacturing technology is often continuous in nature (e.g., co-precipitation, wet-milling, etc.). While there are established technologies for determining concentration in solution of the compound of interest, the real-time measurement of particle-size distribution for the nano range is still not trivial," he states.

Application challenges

The biggest challenge is interfacing PAT to a process, regardless of whether it is batch or continuous. "For the latter, the challenges are of different type, in particular when dealing with small setups; in-line probes may disrupt the process by creating a constraint and/or an opportunity for deposition/precipitation, flow-cell dead volumes may promote back-mixing, etc.," Matos observes. He notes that the opportunity to use higher concentrations (in some cases even running solvent-free reactions) forces the development of strategies to cope with high analyte signals such as automatic dilution strategies or signal attenuation via special probe or flow-cells configurations.

Automated sampling systems that are capable of sampling, diluting, and delivering a representative sample are essential for sensitive PAT techniques such as online HPLC, HPLC-MS, or online GC, agrees Maloney. Due to the variety of different processes that require sampling, a combination of different sampling techniques are often utilized. For example, suspended solids or precipitates in a process may lead to plugging of small-diameter tubing associated with automated sampling devices. Sampling of supersaturated solutions can be challenging and often requires quenching or dilution at process temperatures to prevent solids fouling. For optical technologies such as FTIR, Raman, or focused beam reflectance measurement (FBRM), location and orientation of the optical probe and bench relative to the process can be difficult.

Part of the challenge is also determining what tools are needed when. "In order to achieve the optimum process performance, a 'kitchen-sink' approach is generally used, with as many tools as possible used to investigate every conceivable thing that might happen in a reaction," says Hillier. The other piece is coordination, collection, and dissemination of the disparate data so that it can be analyzed and applied for process control. It is important to assure that the sampling frequency will be able to capture the expected process dynamics and thus process knowledge, and allow proper and timely feedback control, Matos agrees.

Translating PAT data into meaningful information that enables process decisions is another significant challenge. Simple sensors that provide two-dimensional data (pressure, temperature, flow rate) can easily be incorporated into a distributed control system (DCS), according to Bradley Campbell, a research scientist with Eli Lilly. Multi-dimensional data (HPLC, HPLC-MS, FTIR, Raman, etc.) are much more challenging to integrate into a DCS.

"Many analytical technologies that were designed to be bench-top instruments are being adapted for online applications in support of continuous process monitoring. While the analytical instrument hardware was designed with flexibility in mind, the same is not always true for the software. Analytical instrument control, data processing, and reporting software were not designed to communicate with and export data in a format that can be consumed by a DCS," Campbell says. There are currently several vendors looking into this issue and providing solutions for testing, but there is still not a single platform to integrate

FDA: Similar quality violations at multiple Wockhardt facilities

In citing quality control issues found during a Jan. 4–Feb. 5, 2016 inspection at the Morton Grove, IL facility of Morton Grove Pharmaceuticals (a subsidiary of Wockhardt), FDA investigators noted in a warning letter that the violations found at that facility had been found at other Wockhardt facilities from 2013–2017.

Among the problems noted by investigators were unexplained discrepancies or batch failures that were not thoroughly investigated; failure to perform a science-based health hazard evaluation; failure to ensure that laboratory records included complete data; quality investigations performed outside the quality unit's oversight; failure to establish and follow control procedures; and not testing in-process materials during production. In addition, appropriate computer controls were not in place to ensure that only authorized personnel made changes to production and control records.

"At this time, seven Wockhardt facilities (including Morton Grove) are considered out of compliance with CGMP. These repeated failures at multiple sites demonstrate your company's inadequate oversight and control over the manufacture of drugs," FDA stated in the letter. "In your responses to the various actions listed above, including during multiple meetings with FDA, you have repeatedly discussed and promised corporate-wide corrective actions. Yet, when FDA inspects or returns to other Wockhardt facilities, similar violations are shown to persist. Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements."

The agency requested that the company complete a data integrity remediation and a risk assessment of the potential effects of observed failures on the quality of product, and develop a corrective action and preventive action plan.

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all data types into a single data package to use on the manufacturing floor.

Continuous efforts

All of the pharmaceutical industry is working on continuous processing. Waters, according to Hillier, is collaborating closely with not only its pharma customers, but providers of other sampling and software and control systems to develop comprehensive PAT solutions. "Much of our time is spent working with other companies. We are taking an agnostic approach because our customers often have individual preferences for which sampling devices, data analysis software, and control systems they select, and our chromatography solutions need to work with them all," he states.

It is worth noting, according to Matos, that manufacturers of PAT instrumentation are diligently working to improve both the technology and the sampling interface, in some cases via successful partnerships with continuous processing equipment manufacturers. "PAT is not optional for continuous processing. It is necessary for gathering information and establishing an effective control strategy for commercial manufacturing. The increasing interest in continuous processing is creating a favorable environment for PAT equipment manufacturers to push technological advancements in three directions: improving the spec sheets to increase the analytical power of existing and established technologies, adjusting bench equipment for real-time measurements, and achieving further simplification to drive costs down," Matos asserts.

Eli Lilly has focused its efforts on engineering better ways to develop robust process interfaces for integrating analytical instruments to continuous processes and investigating ways to link complex analytical data to DCS systems for the purpose of trending, process monitoring, and control. "In a regulated environment where ideally the technology designed in development can be readily transferred to a cGMP manufacturing facility, care must be taken to ensure that computer systems, PAT, and sample delivery systems are designed to operate in a fully validated state," Campbell notes. Communication between these systems is also essential to enable real-time decision making when more than one data source is providing information on the state of control.

A matter of control

As challenges in process engineering and analytical technologies are overcome, it is vital that PAT data are available to the DCS, process historian, and process control models to enable the development of an integrated process control strategy. PAT data must be visualized within process control charts with the appropriate automation in place to minimize operator intervention and enable real-time decision making when appropriate, according to Campbell.

In addition to the development of control strategies based on PAT, the data-rich environment of continuous processes with online monitoring should eventually allow for real-time release testing (RTRT), according to Matos. "Using physical, chemical, or mathematical analyses, companies will benefit from RTRT from increased assurance of quality (decisions based on more data) and improved manufacturing efficiency (reduced cycle-times, inventory, etc.)," he says.

The CDMO perspective

While the science, technology, and regulatory landscape for PAT use are the same for contract development and manufacturing organizations (CDMOs) and drug manufacturers, the CDMO business model does imply other considerations. "When investigating the implementation of PAT, CDMOs must be assured of a return on their investment beforehand, and thus the technology should be versatile and not product- or application-specific. The concept of modularity and the need for considering the operating costs are certainly part of the decision checklist so that CDMOs can maximize the use of these technologies," Matos observes. On the flip side, the exposure to different products in a high-paced environment creates the opportunity for intensive learning by CDMOs on the use of a given real-time analytical technology for certain applications. **PT**