

Validation and Compliance Software Systems Prepare Manufacturers for Com(PAT)ibility

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BACKGROUND: NOVARTIS; CAPTURE: SPARTA SYSTEMS

FDA's process analytical technology (PAT) framework for pharmaceutical manufacturing and quality assurance **will change the manner in which process data are gathered and reported.** As the industry warms up to the PAT approach, software developers prepare to meet the challenges of successfully carrying it out.

Few people really understand how software works, but everyone notices when it doesn't, especially when these systems contain the data that will be used to determine product quality and ensure regulatory compliance. Industrial-scale software implementation is a considerable investment, and the technology that drives it advances quickly. Thus, it was not surprising that when FDA announced its support of the process analytical technology (PAT) approach to pharmaceutical manufacturing, questions arose about how current software systems would have to be modified.

PAT may be new to the pharmaceutical arena, but chances are that if a company's software isn't set to handle real-time data, then it's already obsolete. What constitutes the "ideal" PAT software system depends on the company's needs, the level into which it is being integrated, and of course

the process under which it will be operating. A system that's too rigid leaves little room for future technologies without the need to conduct frequent and expensive reconfigurations. Likewise, a system that's too "generic" may not perform at the level of efficiency that would justify implementation of PAT principles.

Most software system administrators agree that the right solution will be a combination of off-the-shelf packages as well as customized programming and interfacing. But before the drawing board comes the discussion table. And, just like any other well thought-out plan, a software system design begins with communicating the goals and identifying what will be needed to achieve them.

Data management under PAT

The goal of any software system is to obtain, store, retrieve, and transfer informa-

tion as efficiently and reliably as possible. How these tasks will change in a PAT environment has been and continues to be a topic of numerous discussions between FDA and the industry. As a result of this communication, FDA released in January 2004 its second revision of the draft guidance "PAT—A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance." A large part of the guidance document centers on the method by which data would be acquired and managed to achieve process understanding. Compliance with current good manufacturing practices (CGMPs), in part, will involve assessing whether a company has achieved process understanding by means of process monitoring and control.

Under a PAT system, manufacturers would be encouraged to use the latest proven scientific technologies (i.e., "best practical technologies") in manufacturing as an alternative to traditional, yet less-efficient, practices. For example, batch processing involves off-line laboratory testing conducted on statistically selected samples collected at time-defined points and at the end of each process step. However, the time required to conduct and report the results of these tests may take from several hours to several days. It is not until these tests are completed that the quality of the batch is known. During this time, the batch either continues to the next stage in the process or production is temporarily stopped.

By contrast, the PAT approach involves taking on-line, in-line, or at-line measurements in real-time or near-real time; that is, while the process is occurring. Such measurements allow continuous or semicontinuous monitoring of the quality of the batch and also provide the means of viewing how the process conditions affect the quality.

Quality paradigms. The PAT method of evaluation, which the draft guidance terms "building quality into the product" and also is often referred to as a "quality by design" approach, changes at least three major practices currently used in manufacturing: when quality is evaluated, the type of data that will be assessed, and the volume of data that will be necessary to demonstrate compliance.

First, in some cases, PAT allows the total process time to be defined by a level of quality instead of a time-defined endpoint. For example, the traditional method of blend sampling involves removing a number of samples every few minutes from various locations in the batch, taking these samples off line to a laboratory, testing the quality, recording the result, and determining the variability. "That is the older way of looking at it," says Ajaz Hussain, Deputy Director at FDA's Office of Pharmaceutical Science and Chairman of FDA's

PAT Steering Committee. "Under PAT, you may have a blender with sensor technology and feedback so that you blend until it has reached the level of quality that has been determined, allowing you to move from a time endpoint toward a variant acceptance criteria for that purpose. So it changes the databank quite a bit."

The second practice changed under PAT involves the type of data that would be used to define quality and, ultimately, to ensure compliance with CGMPs. The "quality by design" strategy allows monitoring both chemical and physical data in real time or near-real time. Currently, many analytical tests are univariate tests; that is, testing is conducted as a series of unit operations that evaluate one particular attribute—often related only to the chemistry of the material such as toxicity or to one physical attribute of the finished product such as tablet hardness. Such tests do not take into account the simultaneous evaluation of chemical and physical parameters, the correlations among them, or the affect of process conditions on product quality.

Monitoring a process in real- or near-real time allows operators to evaluate how a change in one or two parameters would affect the overall result and how the other parameters would have to be adjusted to maintain the product within specified quality limits. As observed by Gawayne Mahboubian-Jones, product development manager at Optimal Industrial Automation (Bristol, UK), "Pharmaceutical processes are inherently very complex. In some respects they are probably an order of magnitude more complex than the processes you typically see in the petrochemical industry because we are not looking at simple things such as material purity but rather at complex relationships such as that between particle size and the compression force needed to meet a particular dissolution criteria. And those are very complex models."

As a result of these complex relationships and the correlations that exist among the wide range of process parameters involved, the PAT approach also would change the volume of data that will be required to demonstrate compliance. Says Hussain, "The data that will be under review will depend on the application—whatever would be necessary with respect to evaluating the risk and ensuring that the proposed application is doing what it is supposed to do." Specifically, the current draft guidance suggests that in a PAT environment, the volume of data in a batch record should be "at least half an order of magnitude or more larger" for static PAT-based "classifying" analysis systems than the volume of data required to show CGMP compliance in the current laboratory environment. Furthermore, the guidance

suggests that when “comparable” dynamic PAT-based “classifying” analysis systems are used, the volume of data should be “several times more” than the amount required for static systems.

PAT software: ideal attributes

When finalized, the guidance will provide recommendations, not requirements, to the industry regarding implementation. Thus, the manner in which to implement PAT in terms of software will be left to each company to determine.

Fortunately, because other industries have been manufacturing using the capabilities described in the PAT framework for several years, many of the technical tools to carry out PAT already exist. As Warren Mudd, senior industry specialist at Camstar Systems (Campbell, CA), observes, “In essence, we’re building a system from scratch but our system uses components that have been proven in other industries. The biggest challenge from a software development standpoint is to identify the appropriate technologies that have to be assembled because in many cases there are quite a few to choose from.” Carlos Morgado, associate director at Cimcon Software (Chelmsford, MA) agrees. “The ability of software companies to deliver solutions is there,” he says. “The challenge is to deliver a standard solution to fit the largest number of clients. There may be opportunities to take solutions from one manufacturer to another, but there will have to be some client-specific customization, even if the process is the same.”

Software providers offer solutions on the basis of their clients’ needs. Although there may be more than one solution for the same objective, the general consensus among software companies is that in a PAT-based environment, process understanding will be a key to demonstrating CGMP compliance. In turn, a big part of process understanding is showing that a PAT setup is capable of delivering process monitoring and process control capabilities. Process monitoring involves ensuring that the data acquired are truly representative of the process and of the cause-and-effect relationships among the process components (often referred to as “true correlations”). Similarly, process control means that once a level of quality is obtained, the process is capable of being maintained at that level of quality as needed. Finally, if there is a deviation, the system should not only be capable of detecting it, but, in many cases, it should allow a means to correct it and prevent

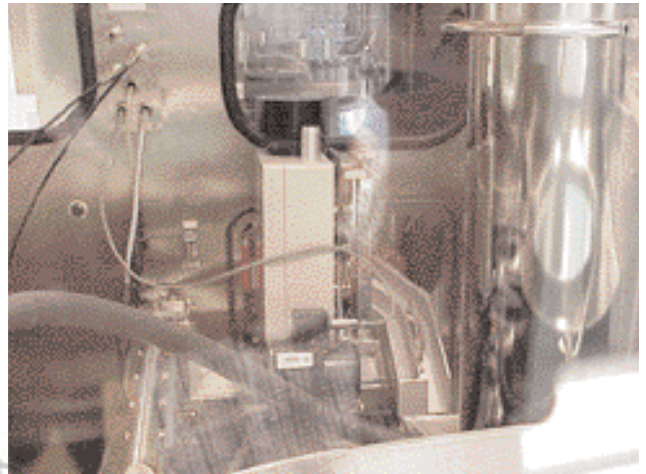


Figure 1: In-line tablet analyzer (AstraZeneca).

it from reoccurring (corrective and preventive action, CAPA).

Software may be categorized as follows: systems operating at the analysis level (e.g., statistical process control systems [SPCs], multivariate analysis systems [MVAs], supervisory control and data acquisition [SCADA] systems); data management packages (for storing, organizing, or transferring data or making the data accessible by other systems); trend analysis software packages or systems (e.g., historian systems); systems or packages that identify and track deviations or nonconformances and that also may be a part of a CAPA plan (quality management systems, quality compliance systems); and multipurpose or “generic” software tools that can be used to interface systems and to integrate processes.

Analytical level. The PAT approach will be most apparent at the points where sensors (also called “process analyzers”) are placed and the data from these sensors are acquired and managed so that the process can be controlled. Some manufacturing processes such as blending and tableting will be more easily adaptable to PAT than others (see Figure 1). According to the guidance, the evaluations generated by process analyzers “must be reproducible, precise, appropriately accurate, and material-representative assessments of the variable factors of interest.” Says FDA’s Hussain, “the process signature will be part of that. And under the PAT scenario the control will be a software control and tailored to whatever the process is.”

Neil Lewis, CEO at Spectral Dimensions (Olney, MD), a company that produces sensors for PAT-based processes, advises that the sensors should be able to produce signals that can be transferred easily into the process control system. In addition, the instrument should be able to measure multiple parameters, and the software

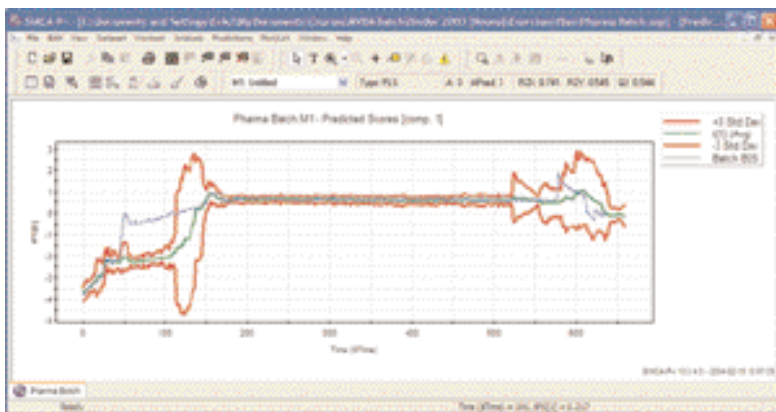


Figure 2: Simca-Batch On-Line uses multivariate techniques and conventional statistical process control to allow users to monitor a batch in process. The above figure shows a real-time plot of a new batch that is outside the control limits (red) (Umetrics).

should be tailored to produce the number of outputs specified by the application. Says Lewis, “there is no theoretical limit to the number of outputs—although there may be some practical limit—as long as the outputs have a measurable analytical signal.” Theoretically, the output from the sensor would go to a process controller that takes that signal and that of other sensors and then all of the measurements are integrated into one process (e.g., an MVA, SPC, historian, or SCADA system). This allows operators to monitor whether the process is operating within specified limits (see Figure 2).

MES level. Typically, the next step after the data have been acquired and transferred to a central, process-control system is moving that information to the level at which it will be tracked, stored, and analyzed along with other data or a standard (“trending”), and/or transferred to the next process step. These are the tasks of a manufacturing execution system.

Camstar’s Mudd recommends that an MES for a PAT manufacturing environment incorporate a number of characteristics. First, he says the architecture should support tight integrations between widely disparate systems such as enterprise resource planning (ERP) systems, laboratory information management systems (LIMS), and electronic content management systems using modern, durable technology such as EAI (enterprise application interfaces) or Web services. The architecture also should allow information to flow quickly and queries to be done on the appropriate information for the analytics to take place. “However,” says Mudd, “the response time has to be predictable in those systems to ensure quality. If an operator requests information about a process, the operator should be able to validate that the response to that query is the valid response. It takes a fairly modern technology from an architecture standpoint to do that. But if it’s done right, that architecture tends to preserve existing capital investments and the company’s

legacy systems and promotes the adoption of LEAN and Six Sigma policies.”

Mudd also points to the importance of an object-oriented core engine with a flexible object library so that small incremental changes can be made in response to new processes without the need for re-engineering or making major changes. “Evolution is inevitable, and as the rate of PAT adoption increases, new technologies in equipment or analytics will need to find their way into the framework. A good MES system should have room to adopt them. You can’t shut the door to using some sort of future technology when it becomes appropriate,” he says.

Other considerations are scalability and multi-site or multicompany accessibility. Notes Mudd, “The system must be able to go from a small-scale R&D environment to a large high-volume production environment without the need for major changes in the computing platform and a complete revalidation of the system.”

Software for quality management and compliance. The information at the MES layer (or, depending on the design configuration, an SPC layer) eventually will have to be transferred to the level where it can be compared against companywide standards. The decisions made at this level will be based on the quality of the data, so the interfaces between this level and all levels below it must be well defined.

In PAT-based manufacturing, these interfaces would be especially vital because considerably larger volumes of data would be transferred to the quality management/quality compliance level. With an increase in the volume of data comes an increase in the probability that a deviation or out-of-specification event will occur, even if, theoretically, PAT should reduce the variability in the data. Therefore, although PAT has minimal effect on the operation of the software at this level, it broadens the scope of the systems’ application and raises the best-practices bar. As Nikki Willett, director of Product Management at Pilgrim Software (Tampa, FL) observes, “Even though we are hoping that PAT is going to reduce the variability of the process throughout manufacturing, there are still going to be nonconformances and changes that will need to be tracked and monitored the entire way.”

Risk management and ERP. Software used for making companywide business decisions, such as those related to risk assessment and management or ERP decisions, will likely be the least affected by PAT. Systems already exist that can collect, process, and analyze these data. As Jim Sabogal, director of pharmaceutical industry business at SAP Labs (Palo Alto, CA) explains, “The major

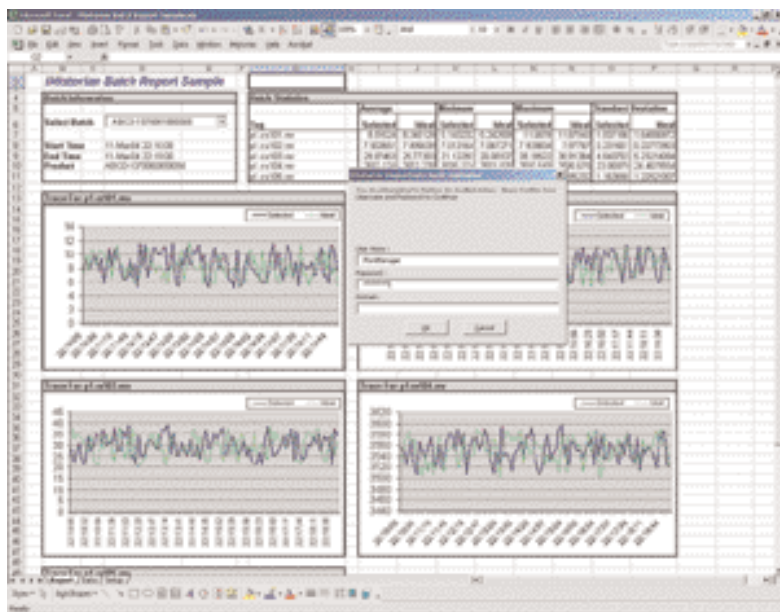


Figure 3: GE Fanuc's iHistorian system incorporates a secure eSignature framework to enable users to deploy and analyze data at a sustained storage and retrieval rate of more than 20,000 events per second. Data can be reported on a common platform such as Excel.

change will be in deployment—what ERP components companies choose to deploy and how they choose to set it up from a process point of view. Each company runs a little bit different between IT and manufacturing.” Software at this level is typically “out-of-the-box” software that provides the flexibility and capability to adapt to process manufacturing changes. Software systems running at this level will require precise interfaces to be in place to provide the right visibility and analysis of the data across the entire company.

The total design

Communication essentials. Software providers agree that the first step toward developing a total design solution that incorporates the ideal attributes of the software at each level is ensuring communication among all parties, including a company's analytical scientists, IT personnel, process and equipment engineers, validation/compliance team, and quality assurance/quality control staff. FDA also has proposed collaboration between the industry and the agency. Says Hussain, “The process is moving forward.” Optimal's Jones agrees, “There is a lot of commitment from the industry to getting standards in place to make PAT work. You can see the process gathering momentum.”

PAT-based process understanding is founded upon the knowledge gained by industry researchers when conducting multivariate experiments (i.e., methodological experiments). According to the guidance, traditional one-factor-at-a-time experiments do not effectively address interactions between product outcomes and process variables. In contrast, experiments conducted during product and process development “can serve as the build-

ing blocks for understanding of the process.” Some software products are already available for design-of-experiments optimization (e.g., Umetrics [Kinneton, NJ] “MODDE” software) as well as on-line multivariate statistical process control (“MSPC”, Umetrics).

Various company personnel also will need to contribute information. Questions that to be answered include

- Where will PAT be implemented and to what extent?
- What are the current (legacy) systems in place at that point?
- What are the current interfaces?
- Will the design be integrated or layered?
- Will a change in one area of manufacturing lead to a negative affect in another area?

A company's quality assurance, LIMS, process engineering, and IT staffs should be involved in developing a PAT solution. As Todd Lybrook, technology director at PharmaTech (Exton, PA) explains, “QA and process engineers know how the process runs, they know where the tricky steps are. You can have greater variability in some steps and still come out with a good quality product. But other steps of the process will be very tight, and you have to be careful to stay within limits. QA also needs to determine new in-line or at-line testing techniques. IT needs to be included to support the infrastructure and the large amounts of data.” Camstar's Mudd adds, “The goal is to understand you're probably not going to get away from the model of laboratory benches in your R&D phase, but you do need to provide a transition from that laboratory bench to what could be called a ‘modern architecture’ with in-line analytics to go to production.”

Building a model. After the appropriate questions have been answered and the user and functional requirements have been identified, then the work of building a conceptual design model can begin. Most software developers agree that the most challenging part of the design solution is at the analytical level, where data are acquired, the process is monitored and controlled, and the analytical data must be transferred. At this level, the multivariate data relationships of cause and effect are developed. For example, when variables *A* and *B* go out of limit “high” by 10%, the system must reduce variable *C* by 25% within 10 minutes or the batch is at risk of loss. Says Lybrook, “The challenge is really going to be at the control system layer where you have automated, validated systems in place—most include individual skids with separate control systems. You are going to have to figure out a way to add extra sensors to give you in-process data and to deter-

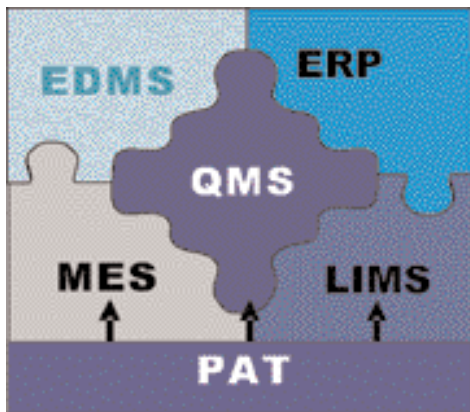


Figure 4: One conceptual software implementation design in the form of a “systems puzzle.” In this model, PAT will link to the MES for any batch record information. It will link to LIMS to provide in-line testing. And it will link to QMS for any OOS or deviation/exception that may require investigation and potential CAPA (Sparta Systems).

mine where you’re going to add them. Are you going to add them in the existing vendor skidded PLCs and potentially cause a problem or warranty issue or are you going to add another layered control system onto what is already there? Then, how is the system going to analyze the cause-and-effect data relationship and react to out-of-limit conditions?”

The design at the analytical level is important because of the effect it will have on the upper-level systems. For example, as Cimcon’s Morgado explains, “If you have a layered design, you may have various automation layers before you have something that is information based, so that everything can be seen at one central point. As you go up the automation layers, the complexity to implement increases, and the more of an impact any change you make will have on the system. From a risk-management perspective, the more automation you put in, the higher the risk will be.”

One possible design approach is Spectral Dimension’s “modular software blocks” that are built to drive each part of the process instrument. The

company’s NIR chemical imaging instrument includes software blocks that drive the camera, the filter, and the multivariate data process. These blocks are then assembled according to the given solution and to the customer’s set of “rules”—that is, the parameters that the company wants to measure (e.g., particle size, temperature) and the statistics or parameter limits. This approach provides great flexibility not only from company to company, but also between products within the same company. Ideally the software package would be integrated with the equipment. Says Lewis, “The hardware is the same; we just adjust how the instrument collects the data and what it does with the data.”

The data gathered by the sensors are then sent to process control systems such as MVA packages, SPC systems, or “historian” type systems. Several companies focus on providing such systems. For example, according to Bob Honor, manager of Life Sciences at GE Fanuc Automation, historian systems provide “the foundation for collecting process data and permit easy and secure access to it as well as making real-time adjustments” (see Figure 3). A data historian system also could be used as an analysis tool for developing correlations of the data via a customized algorithm. That is, it would gather all of the data and conduct trends on that data by plotting one variable against another. Seeing how variables react against each other would provide a model against the data coming in.

Other companies focus on providing system integration and interfacing. For example, Optimal Industrial Automation has designed a data management and control system. The “synTQ” system provides a means of taking the data from a variety of sensors, configuring the data, and then sending it to a prediction engine running on an MVA model, and then using that data for process control. For example, the company is currently working with a facility that in one stage of the process requires data to be gathered from standard and FTIR spectrometers and 11 univariate sources (including eight temperature measurements and two humidity measurements). The focus, according to Jones, is “the real-time backbone” that enables PAT. As Jones observes, “You can’t do PAT without good instruments, and you can’t do PAT without a good MVA package and a good, fast prediction engine that runs with it. But those two by themselves aren’t sufficient. The right data backbone is absolutely crucial.”

Full process control requires the capability to configure data automatically and to run the process as close to real time as possible. An interfacing system should facilitate feedback and feed-forward control such that the data from one stage

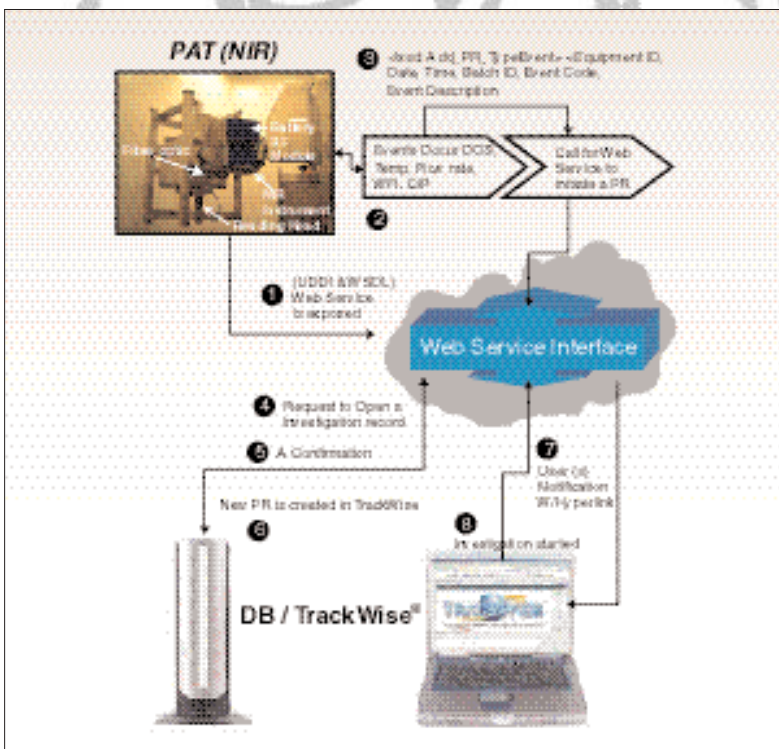


Figure 5: Example of a fully integrated suite that combines NIR sensor on a blending system with a Web services interface to integrate with a QMS system. When an OOS event is detected, a request for investigation is generated (Sparta Systems).

Figure 6: The risk-based approach for integrated compliance supports in-process testing using PAT to improve overall manufacturing and shop-floor product quality and performance (Pilgrim Software, Inc.).



in a process affects the process in a second stage. Optimal builds the interfaces that would be typically required in an overall system design such as NIR spectrometers, A/D converters, OPC servers, and SCADA systems. The prediction engine runs in the background so that, says Jones, “as far as the user is concerned, once you have set this up you don’t even see it happening. All they see is raw data from the process and calculated quality at-

tributes that relate to process understanding. And that, we believe, is precisely the way it should be.”

Designs that incorporate PAT into levels above the analytical layer will vary greatly. According to Rafi Maslaton, COO of Sparta Systems, PAT’s place in the overall software structure is directly related to a company’s existing system (see Figure 4). “Where ERP helps to improve the overall supply chain performance, MES supports the reduction in the batch record release, LIMS to improve laboratories compliance, and QMS to reduce the investigation, corrective and preventive action effectiveness, and turnaround time, PAT will help reduce any process driven quality issues and lack of consistency” (see Figure 5).

One design involves layering the software levels around a PAT-based (SPC) analytical system, with the MES system around it to handle the in-process data, followed by the quality and compliance software to help ensure the documentation nonconformances are handled and submitted. The outermost layer would be a level for risk management, planning, and assessment (see Figure 6).

Another straight-forward design combines MES modules centered on an electronic batch record solution, connected to the PAT data acquisition

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and multivariate model. The "XFP" system (PharmaTech) includes warehouse management, process instruction (electronic batch records, EBRs), materials management, formulation, ERP and LIMS interface, process control/OPC interface, equipment management, electronic weighing, and archiving. The XFP EBR module provides a workflow SFC environment that can accept multivariate data to continue a process (if in-tolerance), loop back, and re-execute a step or execute a new step (if out-of-tolerance). By integrating an EBR module at the MES level, the module has supervisory control over all skids and controllers and can be configured to react to a PAT input and change the process execution.

The right motivation

The PAT road toward quality assurance and compliance is still under construction, and it may be some time before it sees a steady stream of travelers from the pharmaceutical industry. "It's going to be at least a few years before we see any real standard PAT solutions," predicts Morgado. "The biggest challenge for software developers now is how to develop standard solutions that manufacturers will be comfortable in investing, and the biggest concern in the industry right now is just getting more information about how PAT will provide them with a return on investment."

Specifically, there continue to be real concerns in the industry about what the implementation of PAT will mean in terms of cost, time, validation, and regulatory compliance. Many industry experts fear that implementing PAT into an existing process will mean that the already-approved process will be required to undergo additional testing and validation efforts that were not required in the original submission, such as additional clinical trials. However, not many companies are willing to implement the new PAT approach into new drug applications either.

Fortunately, however, some forward-thinking software providers are already set to lead the industry in this new direction. PharmaTech's Lybrook observes that there is a clear distinction between designing a system inherently with good quality and CGMP versus putting a system together and validating it for compliance. "Those

are two different perspectives," says Lybrook. "Normally you would validate a system because you had to, not because you wanted to. For the future, we should think about having the best system with design-in quality. Not because FDA is looking over our shoulder, but because we just should." **PT**

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