This article discusses the critical requirements for a Process Analytical Technology (PAT) data management solution and how these requirements contribute to the successful operation of the PAT solution.

Introduction to PAT Data Management Solutions

by Mark N. Reed

Introduction

This article will discuss the critical requirements for a PAT[1] data management solution and how these requirements contribute to the successful operation of the PAT solution with the end goal of real time product release. PAT Data Management is used in multiple phases of the PAT implementation model. The three phases of all PAT projects are learn, predict, and control. The learning phase comes from the data that is collected, as you "learn" more about your process. The data is then used to build models to "predict" what the process will do when a variation occurs. The model outputs are used to feedback control adjustments to the process control system in the control phase of the project.

First, in the learning phase, there are the process inputs that are collected from the process control system, laboratory analyzers, and the on-line analyzers. When using analyzers, there are software tools in the PAT data management system that allow the user to calibrate the analyzers to accurately detect the substance they are measuring to ensure the quality of the collected data. This calibration of an analyzer to a particular substance is called a method.[2]

Second, there is the storage of this data that allows understanding and predicting of the process. This data storage is performed by an industry standard database (historian) that accepts various input types and formats. It allows the user to pinpoint a specific event or to analyze the data to optimize the process. Chemometricians use univariate or (more typically) multivariate data analysis tools to analyze the data they obtain from the historian. A model that describes how the process is running can be developed using tools that provide outputs to the process control system that then send outputs to final control elements such as control valves and other types of actuators.

In the third phase, the process control system adjusts the Critical Process Parameters (CPPs) to adjust the process to obtain the desired Critical Quality Attribute (CQA) values. These CQAs are monitored and reported to the PAT system in real-time by the on-line instruments and analyzers. Business related attributes also need to be identified and considered as part of the overall PAT process. Visualization is another data analysis tool that allows the operator to inspect a graphic display to find where the process is operating within or outside of the

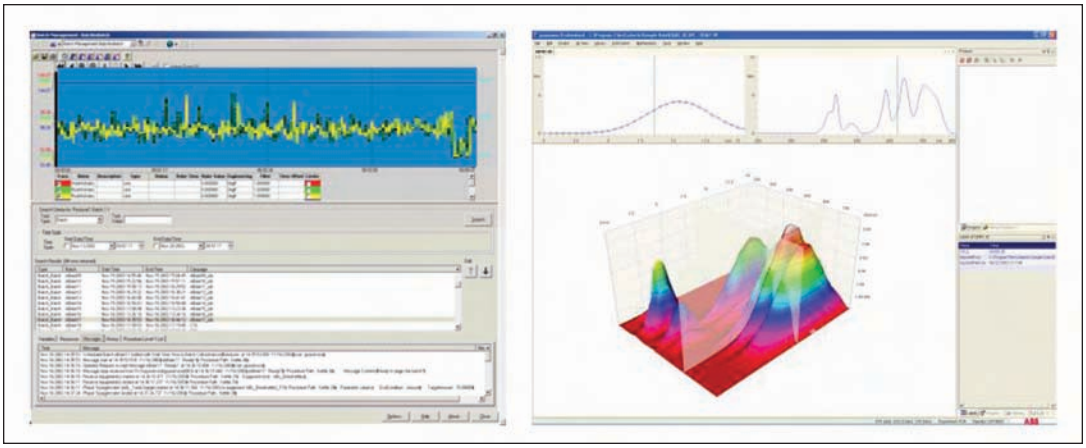

Figure 1. Examples of scalar data (left) and spectral data (right).

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desired state defined by the process design space.

The overall technical requirements to consider in a PAT data management solution that will be discussed are the different types of data that needs to be stored, how the data will be stored, how the integration to the batch management system is done, and what FDA regulations need to be considered.

Analyzer Data for Understanding the Process

There are many options on the market today to measure CQAs in real-time. Facilities may have multiple analyzers from multiple vendors throughout a site. How are these managed? How is data collected? How are the methods managed? Instrumentation and analyzers can be laboratory or process units that have outputs of either scalar (univariate) or spectral (multivariate) data which are available from various manufacturers. There are two categories of outputs that an analyzer presents to the user for measuring the attributes of the process - *Table A, Figure 1*.

Many or all of these are used by life science companies to measure CQAs. FT-NIR is, by far, the most widely used and proven analytical technology for PAT applications.[3] FT-NIR is the most popular due to its noninvasive nature with no sample preparation needed. It uses fiber optically coupled probes; these probes can be remote from the analyzers with several probes multiplexed into a single NIR unit.

Scalar Data	Spectral Data
Pressure	Fourier Transform Infrared (FT-IR),
Level	Fourier Transform Near-Infrared (FT-NIR)
Flow	Ultraviolet-Visible spectroscopy (UV-VIS)
Temperature	Raman
Conductivity	Focused Beam Reflectance Measurement (FBRM)
pH	Continuous Gas Analyzers (CGA)
Particle Size	Gas Chromatography (GC)
TOC	Mass Spectroscopy (MS)
	High Performance Liquid Chromatography (HPLC)

Table A. Examples of typical devices used in process measurements.

Turnkey solutions that utilize these analytical methods on a unit-by-unit basis have been available for years. Unit solutions include reactors, dryers, solvent recovery, crystallization, raw material identification, blending, spray coating, solid dose uniformity, lyophilizations, and many others. However, these analyzers typically do not share a common data format or operator interface and do not easily exchange this

Data Storage

To complete the first step of the "learn, predict, and control" process, data from the process must be collected and stored. There are two basic types of process and laboratory data measurements - scalar and spectra. Scalar measurements are typical process values, i.e., temperature, pressure, flow, pH, conductivity, TOC, particle size, level, etc. that are collected from process measurements and some types of analyzers. Spectral data (spectroscopic raw data) is generated by laboratory and process analyzers, is in the form of multiple arrays of data with timestamps, and is much larger and more complex than a typical scalar signal. Because of its three dimensions, it also is called vector data. Spectral data is collected and used everyday in laboratories and production areas, but is typically set up as standalone equipment with an individual workstation and analyzer or they are connected to a common network of identical analyzers. Rarely is the spectral data combined with data from other types of analyzers or from a process control system in a single database that allows an analysis from multiple data streams or allows ease of data retrieval.

A data manager to collect and store information for discrete, continuous, and batch processes should be structured according to the procedure and associated with the lot (batch or work order) ID. Lot information should include all spectral and scalar data and the metadata with which it is associated. This includes data from control recipe execution, operator actions and comments, process alarms/events from equipment acquired by batch, runtime changes, the methods that the analyzers used during their analysis, version control of the methods, the spectral data from laboratory and process analyzers, and the scalar data from the process. By storing the data in a format that associates it with the lot, it is easy to display and/or report any information from a specific lot or from an entire campaign. This retrieval would take advantage of today's batch engines that use an ISA-88 model that defines a data structure for recipes, equipment, schedules, and history, along with integration to enterprise applications. This allows complete ease of recalling and using the data, as it is the same format as the process recipes and analyzer PAT methods.

To complete the second step of the "learn, predict, and control" process, the information learned during the first step must be organized and modeled to form a set of predictions for various process changes. After collecting the CQAs, tools are used to model the multivariate data to create predictions that characterize the batch - *Figure 2.* The output from this modeling identifies the status of the batch during each process step and predicts its output to the next process step and to the last process step that delivers the final product. Comparing predicted values from the current batch to a set of values recorded from acceptable batches provides a tool for assuring the quality level of in-process batches. This can be called operating to a golden batch, within the control space, or can be classified as Advanced Process Control (APC), but the result is the same; a way to predict the outcome of a batch based on the real time process measurements.

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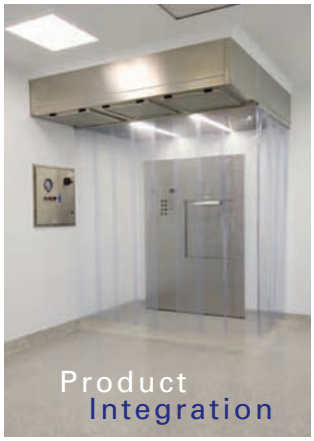

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data with the plant's process control system and historical systems. In addition, the analyzers sample the process and produce results on different time frequencies determined by the amount of time the sampling takes and the sampling needs of the process. In a typical facility using these unit PAT operations, using multiple analyzers lead to large amounts of manual collection and correlation of the data from the facility's "islands of information." Having a system to provide a common user interface and common method development tool for different types of analyzers would enhance usability while reducing the system's training and long-term support costs.

On the topic of data, the FDA states:

"Process analyzers typically generate large volumes of data. Certain data are likely to be relevant for routine quality assurance and regulatory decisions. In a PAT environment, batch records should include scientific and procedural information indicative of high process quality and product conformance. For example, batch records could include a series of charts depicting acceptance ranges, confidence intervals, and distribution plots (inter- and intrabatch) showing measurement results. Ease of secure access to these data is important for real time manufacturing control and quality assurance. Installed information technology systems should accommodate such functions."[4]

An analyzer has a calibration associated with it that is comprised of a collection of spectral data and a customizable set of parameters describing a particular analysis procedure. These calibrations are used in quantitative and qualitative analysis either to find out an amount of a particular substance contained in a sample or to prove the identity of a substance or compound. Based on these pre-calculated results, reliable predictions for the identity of or an amount of a substance in an unknown sample can be made.[5] Calibration methods are used to control a set of calibration models that have had corresponding discrimination criteria introduced to them to avoid model selection problems and misleading result interpretation. Prior to a particular lot being started, these methods must be downloaded to the analyzer and confirmed by the

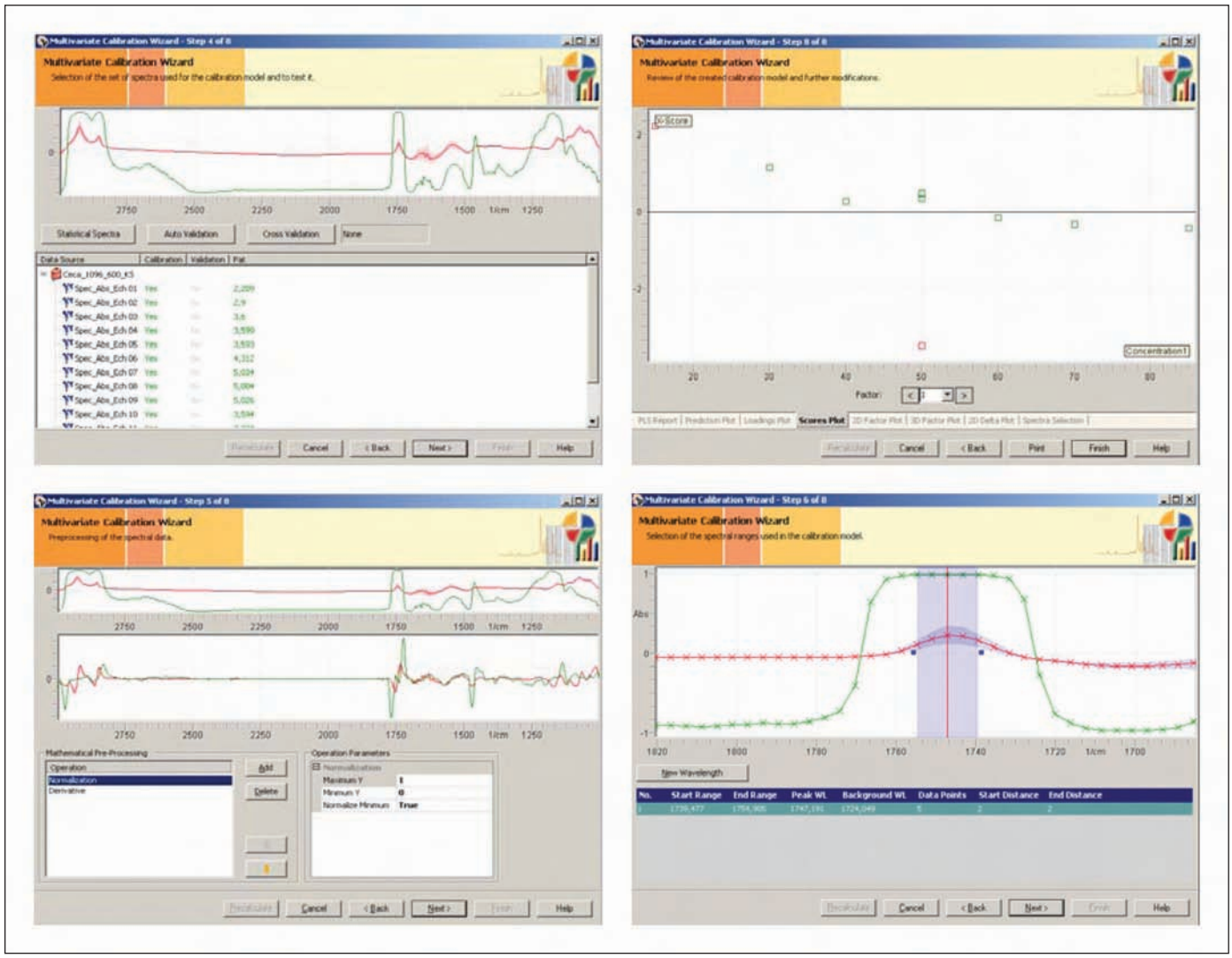

Figure 2. Example of multivariate model builder tool for data analysis.

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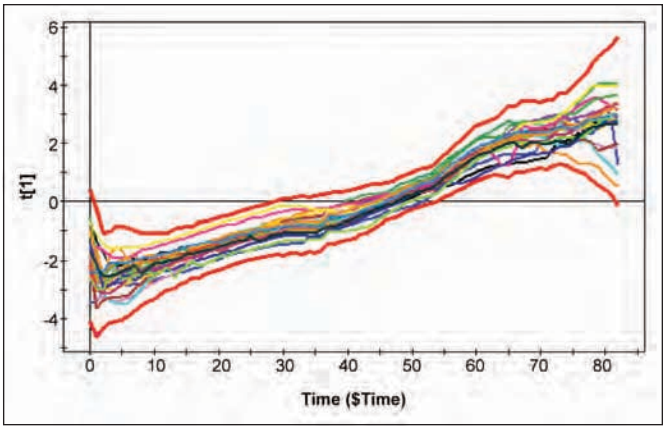

Figure 3. Example of batches that have run within their control space. (Control space graphic courtesy of Umetrics Inc.)

analyzer controller before analyzing samples. One function of the PAT data management system is to store these methods along with the audit trail confirming that this action has taken place for the lot that is preparing to run. The known method is necessary to validate the data collected from the analyzer during the lot.

When using multiple analyzers from various vendors, the complexity of managing the methods and correlating the data can grow rapidly, soon reaching a point at which it can be questioned if the results from the activity are worth the effort. Viewing the data also can be challenging when using the different tools and formats that are delivered with the various vendor's analyzers. A PAT data management system that delivers a common format and approach for viewing the data from the various analyzers with a single tool saves time, money, and reduces mistakes. Another potential problem with combining data from multiple instruments is that the data from different types of analyzers will typically be produced over various durations and on different schedules. One analyzer may be producing results every 10 seconds, another analyzer may be producing results every 60 seconds, and the associated process control system instrumentation may be providing sample data at intervals of less than five seconds. All of this data is time stamped, but aligning all this data for use in analysis and feedback control is a critical requirement for accurate data analysis and modeling. If this time alignment of data is done manually using the time stamps, it can be very time consuming and prone to errors. Storing the data in a data management system that automatically aligns the data by time and by lot, reduces the errors from manual transcription and improves the process for using the data for real-time feedback control by ensuring that the process is being controlled using the correct data and proper calculations.

Control System Integration for Controlling the Process

Once the scalar and spectral data is stored and time aligned

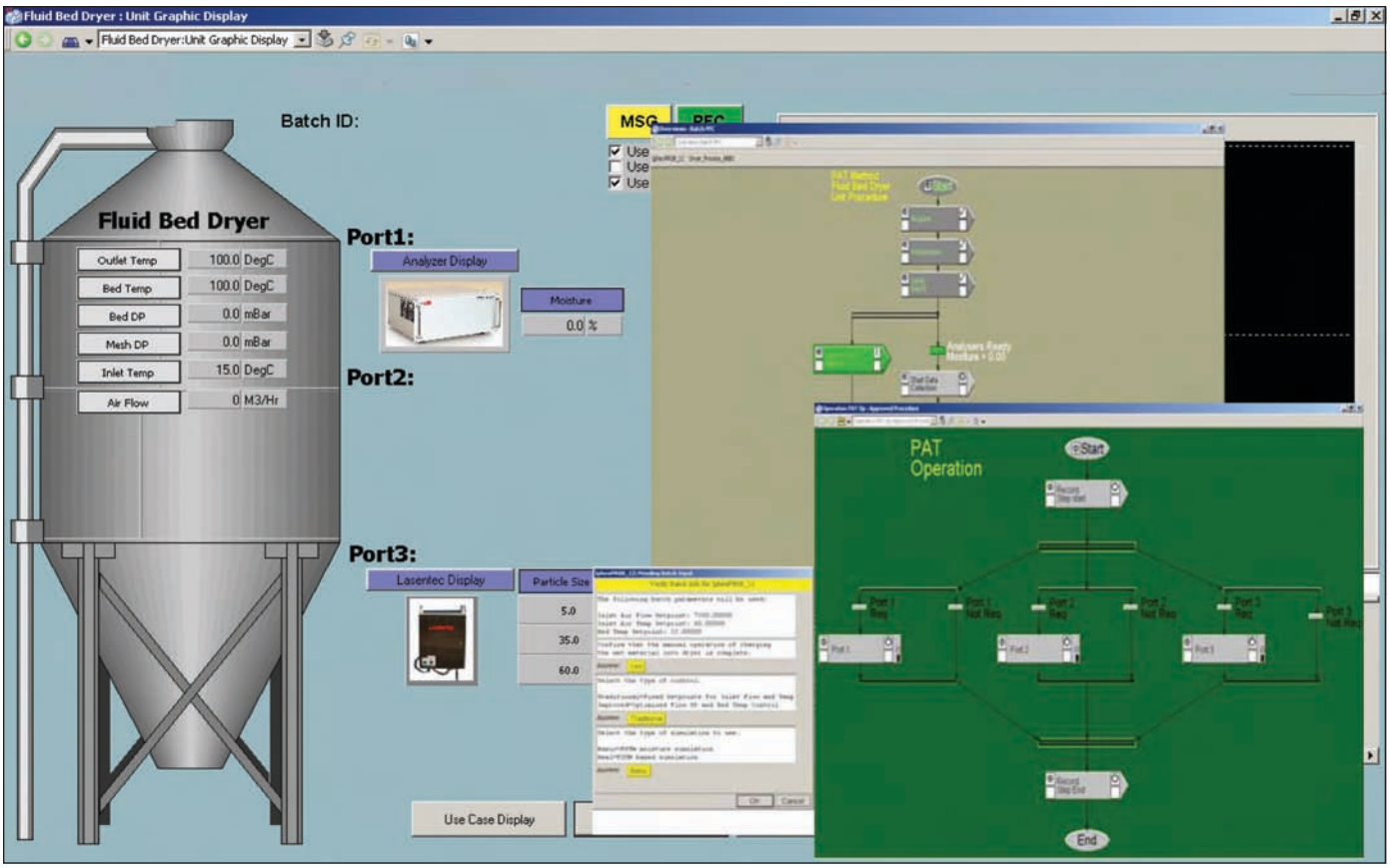

Figure 4. The graphic shows an operator control graphic with the unit procedure and the PAT method. The PAT method is embedded in the unit procedure.

in a data management system and the methods associated with the data are completed, a process model can be built using various tools available on the market. The goal of controlling the process is to identify the "control space" that defines the limit of the process system's control capabilities and the "design space" for the process parameters that defines the limits of the process that must be observed to maintain the desired output. The goal is accomplished by measuring the CQAs and controlling the CPPs to maintain the system in a safe state, where the process parameters are well within the defined design space or window of constraint of the process. Setting up a well-managed data collection system, as mentioned above, delivers information that can be calculated from the data to provide a continuous state of monitoring and control of the process.

Visualization on the control system is used to view both the scalar and spectral data to assist operators and supervisors in defining where the process is located within the process's "control space." The integration of the Data Manager with the control system makes this visualization possible. This integration allows the operations staff to see the process data and its association with the CQAs that were previously defined for this process. It also allows for the monitoring and comparison of the process to that of a previously produced successful ("golden") batch so that the exact recipe and procedure may be repeated - *Figure 3*.

Modern control systems can be configured to provide advance alarming capabilities or asset monitoring once the process is defined, modeled, monitored, and controlled. Asset monitors can take various inputs from the process and/or analyzers and record asset performance over the entire life span of the asset for comparison to a golden standard. Subsequently collected information can help managers set future performance and profitability goals. Using asset optimization programs with these asset monitors also can enable the plant to significantly reduce costly production interruptions by enabling predictive maintenance. When integrated with SMS and e-mail messaging, asset optimization provides a method for sending messages based on alarm and event information to chemometricians or application scientists via cell phones, e-mail accounts, and pagers. This process expedites the use of the data by system development personnel to improve the process.

In order to maximize flexibility for manufacturers and to have a standardized approach for this flexibility, manufacturers utilize the ISA-88 batch model to control the process. This ISA-88 model can be used for both continuous and batch processes. Even though a process is running continuously, there is a need to "track" lots of materials, utilities, and environmental and process conditions. This method allows an efficient way to do this plus optimizes date retrieval time. Using this approach increases product consistency, allows easy

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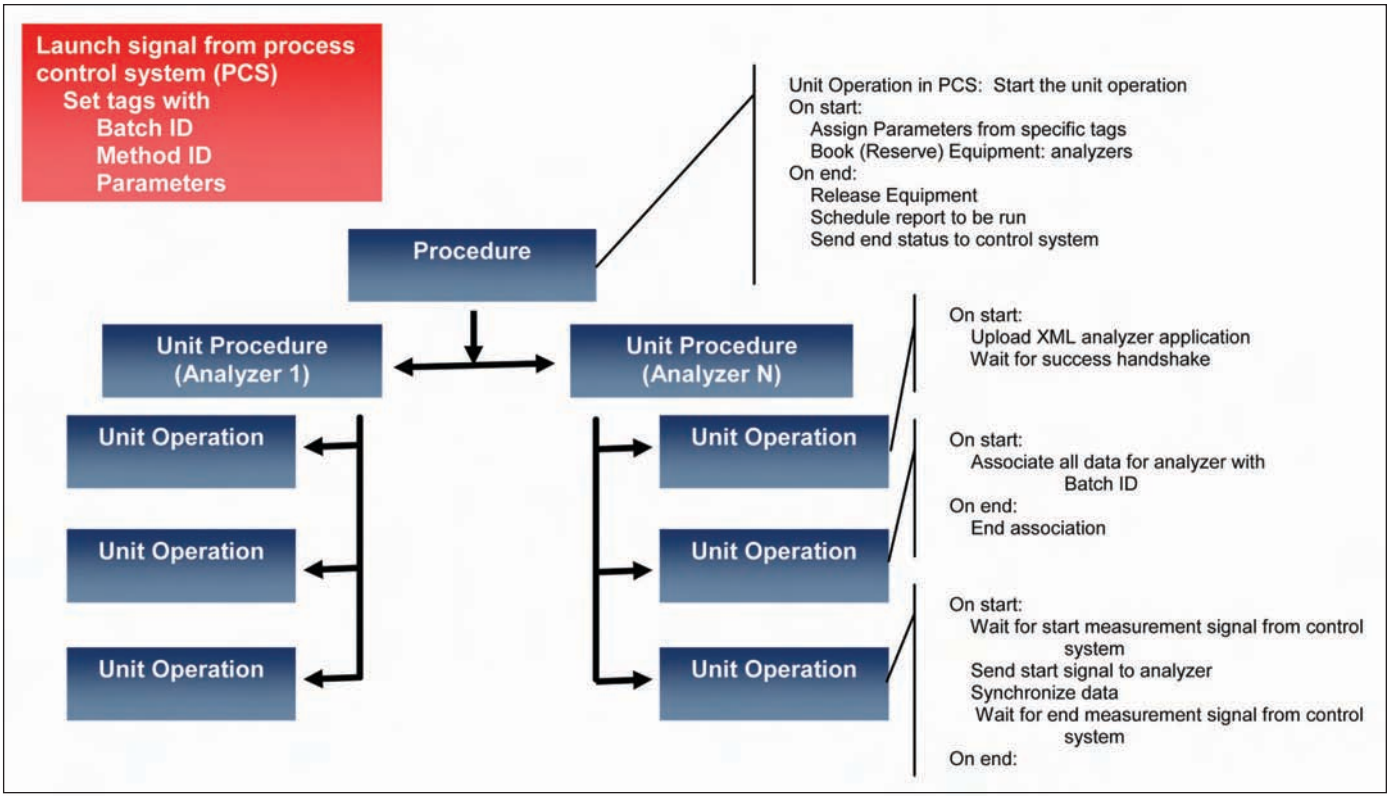

Figure 5. Example of complex PAT method in ISA-88 format.

to use recipe management operations, integrates production management functions, maximizes equipment utilization, and confirms regulatory compliance. Process batch management functions include product definition management, production execution management, production resource management, production data collection, and production dispatching.

The product definition management function includes information such as procedures, formulas, equipment requirements, and headers. This is the area of the ISA-88 model where the analyzer method can be integrated into the overall process. A procedure function chart is the graphical representation of a procedure - *Figure 4*. Each step of the procedure is displayed by a unique combination of colors and symbols.

For a process with spectrometer analyzers, there is a need to integrate the analyzer configuration step into the overall procedure. A field proven PAT method combines the analyzer configuration and batch procedure combined into one ISA-88 format file. A Process Control System (PCS) controls the execution of the PAT Method as the master control in the master/slave relationship between the control system and the PAT Method. This integration allows the control system to "book" the analyzer, download the method (parameters), confirm that the analyzer has the correct method installed, start the data collection, store the data, and end the data collection operation. Having an "end collection" operation to stop the collection of data when the process is completed reduces storage of unnecessary complex spectral data and increases the storage efficiency.

Storing the analyzer method with the lot data being collected from the analyzer eliminates any doubt as to which method was used. All the data from the analyzers, the method(s) used, and the other process data associated with the lot (temperatures, pressures, flow, levels, pH, conductivity, TOC, etc.) will be stored in a batch folder associated with that lot that is located within the data management system. This batch record has a "software wrapper" around it that prevents changes to the data and provides easy access to the data via the system's network or the plant or company's intranet.

A simple PAT method is where one analyzer is used in a unit operation. A complex PAT method is where two or more analyzers are used in a unit operation or when stream switching is performed based on the product (recipe) that is being run. The modular nature of the ISA-88 format allows complex PAT methods to be easily integrated to complete the PAT solution - *Figures 5 and 6*.

An interface is required for each spectrometer analyzer integrated into the system. The communication between the system and the different analyzer components used to measure a process can be challenging. There are many different analyzers being used in the industry today, manufactured by various vendors, and using many different communication protocols integrated with many types of process control and information systems. Currently, there is no standard communication protocol for analyzers to match the standards that are available for other instrumentation, i.e., Profibus and Foundation Fieldbus. The OPC Foundation has responded to this challenge by recently starting a working group, OPC Unified Architecture – Analyzer Device Integration (OPC/UA – ADI)[7] to develop a standard for analyzer interfaces. Several analyzer manufacturers and end users are represented on

the team driving this effort to a standard protocol interface. In the meantime, a standard generic analyzer controller has been developed that allows all different types and brands of analyzers to communicate to the batch manager that is described above.

Completing the third step of the "learn, predict, and control" process allows the process to be continually adjusted to maintain a high level of quality based on the measured values and predictions generated in the first two steps. This is only possible after the process has been clearly understood, with all the variables known and the CQA's reaction to changes in the system CPPs known so that it is possible to produce a product safely and efficiently by using closed loop control - *Figure 7*. Current closed loop control is set up so that the recipe management system controls the system CPPs by sending inflexible recipe setpoint parameters to the control system. With the proper PAT tools in place and properly set up, the system can monitor the process and modify the CPP values based on knowledge of the CQA's reaction to the changes to adjust the process and keep it within the guidelines of the design space that was previously determined.

The PAT enabled control system adjusts the setpoints of the PID algorithm or phase logic that is embedded in each of the controllers to keep the process within the specifications of the design space rather than maintaining the recipe setpoint. The system continues to collect and model data from the laboratory and process analyzers (CQAs) and the process instrumentation as it is stored and time synchronized.

Compliance with FDA Regulations

Any electronic data management application used in the life

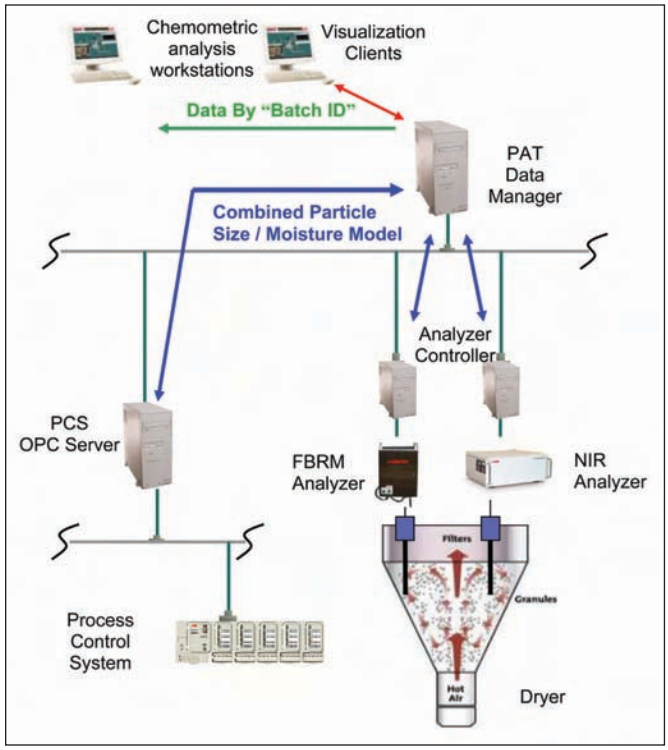

Figure 6. Example of complex data PAT solution with PAT Data Management Solution.

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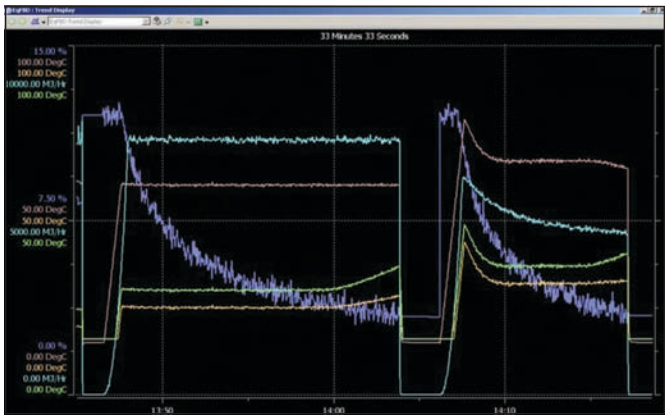

Figure 7. Trend display shows time elapsed during runs of a dryer, the first one without advanced model control, the second one with advanced model control.

science industry for GMP operation in a pilot plant or manufacturing facility must comply with the FDA requirement 21 CFR Part 11.[8] This regulation defines the use of electronic records and electronic signatures in the industry, including the role of validation, time stamps, copies of records, and record retention in the regulation. There are a number of software applications on the market today that can perform portions of complete PAT data management solution; however, each portion must comply with the applicable FDA predicate rule and 21 CFR Part 11, and the overall system also must comply. A system approach to PAT data management is the preferred approach due to ease of compliance, reduced cost of validation, single source responsibility of the supplier, ease of updates and upgrades, and the reduce cost of implementation.

Ease of validation is one of the major advantages of using a single system approach to data management. A system that uses a single database for data collection and data and metadata storage can be validated more easily than a system composed of multiple databases and software packages that have been integrated on a project-by-project basis. A system with multiple databases will have multiple interfaces, and each of these interfaces have to be qualified. Using today's technology to develop a single system that controls multiple classes of analyzers, performs data collection and data calculation functions, and has interfaces to external information technology and control systems can realize a significant savings in the cost and time spent validating the installation. This modular validation effort allows the reuse of the validation for the R&D and pilot plant applications in the manufacturing sites without extensive revalidation; a quick installation verification is all that is required to qualify the reused method. It also is possible to use analyzers that allow transfer (reuse) of calibrations between individual devices due to their tight manufacturing specifications.

Benefits

There is no lack of information concerning the savings associated with using PAT. The petrochemical, pulp and paper, and electronics industries have been doing this type of automated adjustments to the processes for many years. Recently, the FDA has asked the life sciences industry to perform the same process control. In addition, a series of guidance documents have been created by global regulators, including "Pharmaceutical cGMPs for the 21st Century," "PAT Initiative Framework," and "ICH Q8," as well as a renewed interface with industry groups such as ISPE, PDA, and IFPAC.

The ISPE PAT Community of Practice (COP) has a discussion thread on the ISPE Web site that contains various benefits from using PAT, including:

- better understanding of the process
- increased reproducibility from batch to batch
- reduced process risk
- reduced validation and revalidation effort
- reduction of scrap
- higher throughput

Using PAT is not limited to the manufacturing area. A complete PAT plan should include its use in R&D and pilot plant areas as well as in the manufacturing area. Ideally, PAT principles and tools should be introduced during the development phase.[9] The process understanding gained during the development phase of the product, including an understanding of process changes due to variables and raw material changes, can be transferred to pilot plant and manufacturing areas. This will allow the user to maximize these process benefits as they progress through scale up, testing, validation, and manufacturing phases.

With an integrated PAT data management program, qualified PAT methods can be transferred from one facility to another for identical processes. With some analyzers on the market, this also can include the calibrations of those analyzers.

Summary

Advances in process analyzers and PAT data management systems make it possible to perform real time process control and online quality assurance during the R&D, pilot, and manufacturing phases of a product. This discussion covered several topics and various areas of a typical facility and the multiple disciplines needed to fully implement a PAT closed loop control system that delivers the most desired benefits. Storing data in a format and method that supports PAT implementation and use is not a simple task.

This discussion identifies that it is most useful when the PAT solution can be found in a single, scalable solution that interfaces with multiple types of analyzers, historians, and control systems, can support time synchronization, and store the PAT methods and data in a single batch file following an ISA-88 format that is compliant with current FDA regulations. A comprehensive PAT data management system must be in place to fully realize the benefits available from a full service PAT offering.

A PAT data management solution gives the user all the tools necessary for a PAT project. The results from a correctly set up PAT data management system allow understanding and optimization of the process. Having a system to provide

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a common user interface and common method development tool for different types of analyzers enhances usability while reducing the system's training and long-term support costs.

Once the PAT data management solution is in place, the user will be able to understand where their process is within the control space and will be able to control it within the necessary limits. A fourth phase of a PAT project then can be added – continuous learning and optimization of the process based on the data. This understanding and optimization can result in increased yields and throughput, and reduce costs to support the ultimate goal in manufacturing: Real-Time Product Release (RTPR). All of these functions must be accomplished using software that can be configured to meet FDA regulations.

The FDA states that Real-Time Product Release can be enabled by PAT:

> *"real time release is the ability to evaluate and ensure the acceptable quality of in-process and / or final product based on process data. Typically, the PAT component of real time release includes a valid combination of assessed material attributes and process controls. Material attributes can be assessed using direct and / or indirect process analytical methods. The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release of the final product and would demonstrate that each batch conforms to established regulatory quality attributes. We [FDA] consider real time release to be comparable to alternative analytical procedures for final product release."*[10]

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About the Author

Mark Reed has more than 27 years of experience in automation system sales and design for pharmaceutical, biotech, chemical, and other industrial facilities. For the last 24 years, Reed has worked for ABB Inc. (previously Taylor Instrument and Combustion Engineering) as a Principal Account Manager specializing in automation systems for the life sciences and chemical industries. ABB is one of the world's largest suppliers of process automation and building management systems, PAT, drives, robotics, analytics, instruments, and project services to the Life Sciences industry. Combining world-class products with deep application and industry experience, ABB helps customers achieve higher levels of operating efficiency, quality, and compliance. Reed has been actively involved with the successful introduction and sales of each of ABB's automation systems. Currently, he works with ABB's PAT Data Manager product and process analyzers to assist companies in realizing the benefits of using PAT and process analyzers. He graduated with a BS in chemical engineering from North Carolina State University in 1981. He is a member of ISPE and ISA. He can be contacted by telephone: +1-404-281-3543 or by email: mark.reed@us.abb.com.

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