

Integration guaranteed

Taking Process Analytical Technology (PAT) to the next level

Chris Hobbs

In the pharmaceutical industry, it takes approximately 12 years to bring a new drug to market at a cost in excess \$800 million! While this is without doubt a staggering figure, it looks set to increase because new pharmaceutical products, which are more focused on what they can treat, cost more to develop. The overall result is increased development costs with less return. However this increase in investment does not seem to have had any impact on the number of New Chemical Entities (NCE) being approved. In fact, the approval rate is in decline. In addition, increasing costs have forced the industry to look at new and innovative ways of becoming more efficient, both in the creation of new drugs and the production of existing drugs. One of the leading initiatives, which does seem to be making an impact, was launched in 2002 and is called Process Analytical Technology (PAT). At the heart of any PAT system is the process analyzer. However, the availability of multiple analyzer platforms and the absence of some form of standard for exchanging data has resulted in the creation of "islands of PAT."

The problem – until now that is – has been the lack of any form of integrated solution. Over the last few years ABB has worked closely with leading pharmaceutical companies culminating, in the release of the ABB's Industrial IT for Process Analytical Technology in 2007. This scalable purpose-built solution meets the key requirements of a truly integrated PAT solution.

Process Innovations

Pharmaceutical manufacturing processes are highly complex. Quality, yield and the cost of operation are affected by the interaction of many variables. Yet performance improvement has never been more critical to success and survival, and achieving this depends largely on how well the complex variability of the process is understood. In the pharmaceutical industry, process analyzers are used for this purpose, as well as to ultimately control quality variations in the production process. Analyzer technology has been used successfully in both the R&D and production life cycles on single-unit operations, such as blending and drying, and it is playing an increasingly important role in identifying and understanding the variations that occur between laboratory and production equipment during scale-up. Such is the impact of this technology that it became a central feature of the PAT (Process Analytical Technology)¹⁾ initiative launched by the Food and Drug Administration (FDA) in 2002.

Five years on and this initiative has resulted in analyzer companies and third-party integrators providing their own stand-alone PC solutions capable of controlling single-unit operation, and which can export predicted values (such as moisture content or average particle size) to third-party DCS and SCADA systems. To put it another way, various PAT analyzers exist that can be used in unit operations such as reaction monitoring, fermentation,

blending and drying. However, the availability of multiple analyzer platforms and the absence of any real standard for exchanging data has led to the creation of “islands of PAT.” Gathering information from separate unit operations is complicated by the fact that all analyzers have different user interfaces and data formats. To overcome this, there is a need for new tools to execute complex PAT methods using a standard and PAT-friendly interface.

PAT – the next level

Recently, pharmaceutical companies have been investigating the possibility of using analyzer-based control so that traditional batch processes can be run in a continuous manner. For this to work successfully, the coordination of multiple analyzers measuring different types of data from multiple unit operations is required. Tight integration with existing control and information technology is needed to control and maintain an electronic record of the production process.

Joint ventures between process control and analyzer companies have resulted in bespoke solutions that have contributed to achieving this goal. However, fundamental differences in data types as well as the quantity of data collected have stressed the traditional control and data management environments. Analyzer platforms produce large amounts of data of differing formats (eg, spectra, bar graphs, chromatographs and images). These

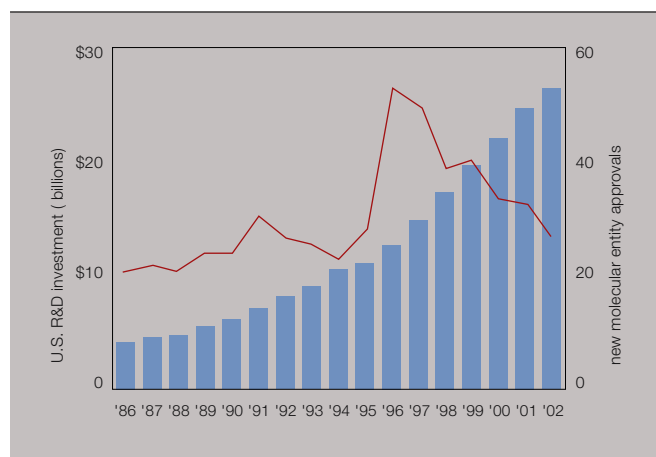
in turn require large array-storage facilities that are over and above that which is normally available on a DCS or SCADA historian. The acquisition of knowledge data from different analyzer platforms must be synchronized with data from other third-party systems, such as DCS, SCADA and LIMS, and stored in a structure that is defined by a particular production model (eg, S88²⁾ Batch control standard). Finally, the data needs to be easily accessible to third-party manufacturing management systems as well as to other lifecycle management and regulatory systems to create what is known as a Collaborative Production Management (CPM) environment, linking the process through to the production management system. In short, an integrated and flexible IT environment is needed to make this possible, and the good news is that such a solution now exists.

Just what the industry ordered

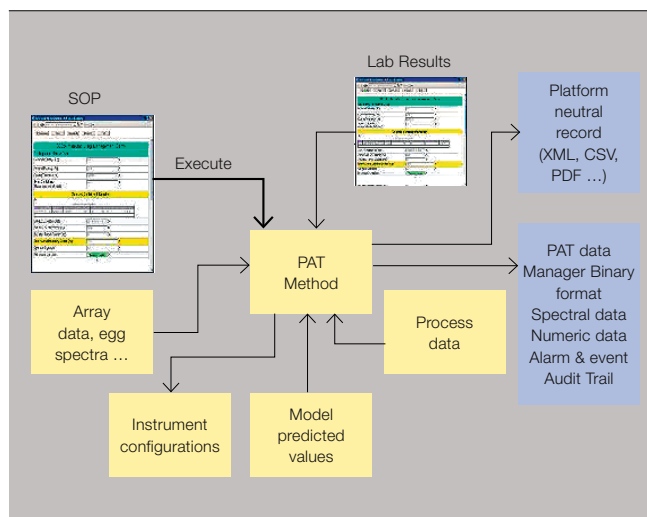
ABB is both a control system and analyzer solution supplier, and over the last few years the company has used its knowledge and expertise in these

Despite a massive build-up in research funding, the number of new treatments approved each year has fallen.

(Source: Datamonitor, PhRMA)



1 The PAT Method



Footnotes

¹⁾ “PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (ie, during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.” (www.fda.gov/Cder/OPS/PAT.htm, October 2007)

²⁾ S88 is a standard addressing batch process control. It is a design philosophy for software, equipment, and procedures.

areas to form successful collaborations with leading pharmaceutical companies. These collaborations have culminated in the release of *ABB's Industrial IT (IIT) for Process Analytical Technology* in 2007. This scalable purpose-built solution meets many of the key requirements of a truly integrated PAT solution including:

- A common Human Machine Interface (HMI) for all analyzer types.
- A data exporter, which allows the extraction of synchronized single-point and array data collected from multiple analyzer platforms by specified equipment or the direct transfer of data to third-party modeling packages.
- A universal adaptor to allow for ease-of-interface to new and existing analytical devices.
- A central PAT configuration method including version control.
- A central S88-type data storage for all data and data types including array (eg, spectral or histogram), predictions, statistics, alarm, event and audit trail.
- The ability to operate multiple analyzers/analyzer channels at the same time over multiple unit operations.
- The ability to pause and reconfigure an analyzer during the execution of a PAT procedure, while other analyzers remain operational.
- Supports the use of electronic signatures.
- It is aligned with ICH guidelines 8, 9 and 10 (draft).

A truly integrated approach

With ABB's solution, a user can start with a single-unit operation before scaling-up to accommodate multiple analyzer platforms distributed over multiple unit operations and production plants. It can function stand-alone or with existing DCS/SCADA platforms. In addition it can integrate seamlessly with ABB's own System 800xA Distributed Control and Safety System.

To overcome the problem of interfacing to many disparate analyzer data formats, ABB has created standard drivers to allow existing and new analytical devices to connect to the FTSW800 Analyzer Controller Platform. This is further enhanced by a tool kit enabling third-party integrators or other analyzer platform vendors to create their own interface to the ABB standard.

ABB's Industrial^{IT} for Process Analytical Technology eliminates the so-called "islands of PAT" by creating integrated process based solutions.

Developing data standards

For a truly integrated solution, the data exchange between analytical devices and third-party platforms needs to be seamless. This can be achieved if a

common standard exists that defines the approach. ABB has been behind the formation of an OPC³⁾ Foundation Working Group whose purpose is to define a standard approach of interfacing analyzers over OPC UA (Unified Architecture). The vision of the group is to provide a means for vendors to write standard device drivers that publish the capabilities of process and laboratory analyzers over OPC UA data links. These drivers will allow complete access to all low-level and high-level data, and will be compatible with regulated manufacturing environments. In particular the OPC working group has been formed to focus on the PAT requirements for the life sciences industry.

Managing the data

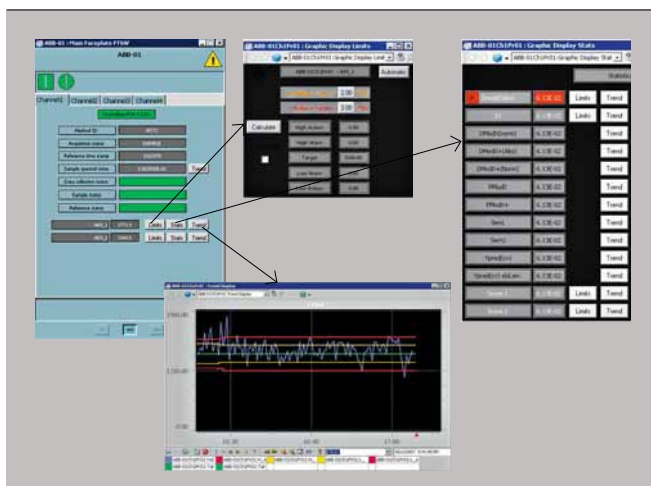
If PAT data is to be useful, it should be stored in a structured and regulatory compliant manner so that it can be easily viewed, exported and validated. Typically this requires knowledge of what stage the process is at, and which process equipment, equipment port, analyzer and analyzer channel is in use. Because not all analyzers function in real time – and those that do may be sampling at different time periods – the data must be synchronized to provide a common time-frame reference.

In order to achieve this, ABB has included a Data Manager within its

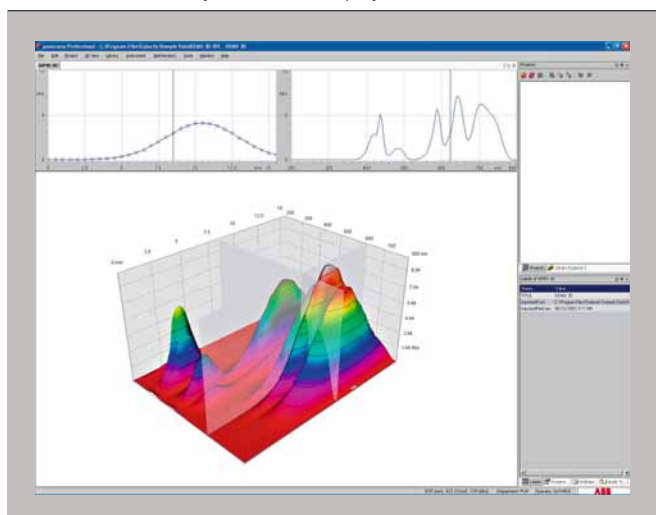
Footnote

³⁾ OPC is a standard communication protocol.

2 Preconfigured trend displays allow easy access to model predictions and their associated scores and statistics



3 The PAT Data Analysis tool can display data in 2D and 3D views



Process Innovations

IIT PAT solution. This Data Manager ensures that all data is stored in an S88-type manner. Adhering to S88 guidelines means the information concerning the location of an analyzer probe, as well as the batch the analytical data belongs to, is also included. Data is stored by time and date using an enhanced history engine which is capable of storing a mix of formats, including array (spectral, chromatograph), single-point (predictive values and their associated statistics) and event (alarms, audit trail) information. Such a combination ensures that PAT Method data can be easily identified by batch, equipment, analyzer and channel. Finally, the addition of a dedicated export engine allows the user to export data, using the same S88-type structure, in formats that are compatible with third-party modeling packages.

The PAT Method

A PAT Method **1** is a set of instructions that dictate the operation, development and validation of the analyzer-based models. These models in turn monitor, predict and control the Critical Quality Attribute (CQA).

The PAT Method is configured graphically **2**. A PAT Method describes the production area and analyzer equipment that will supply the data, and dictates the data storage structure and analyzer configuration required. It is version-controlled, and a standard set of libraries based around analyzer types enables quick and efficient configuration. The PAT Method can operate as a

stand-alone feature or it can be externally triggered from third-party platforms, such as existing DCS/SCADA systems or batch managers.

Data visualization

The PAT Method can be scheduled or triggered remotely by OPC tags, and once running, its progress may be followed using the Procedure Function Chart tool. Analyzer information is then forwarded to standard library face-plates and graphical displays⁴. As well as raw data values, meta data such as PAT Method name, version, equipment name, port name and key diagnostics from the analyzer are also displayed. Preconfigured trend displays allow easy access to model predictions and their associated scores and statistics **2**. Preconfigured warning and alarm levels are trended to give an early indication of quality deviation.

Data analysis and model building

ABB provides its own PAT data analysis tool and the ability to export data to third-party tools. This data analysis tool:

- Provides data mining of PAT Method data
- Displays analytical data
- Provides 2D and 3D views of the data **3**
- Provides wizard-driven univariate and multivariate model builders
- Supports MLR, PLS1, PLS2, PCA and PCR models

Exporting data

There are a number of different modeling and analytical packages available that will only accept data conforming to some common synchronized format. Achieving compatibility entails some form of manual and time consuming data extraction and alignment activities which, most likely, requires the use of additional software.

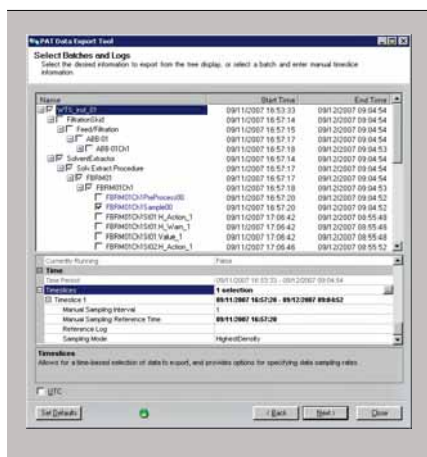
ABB's Data Export tool overcomes this problem by exporting PAT data from running or completed PAT Method procedures in formats that are compatible with existing packages, such as ASCII (tab or comma separated) or GRAMS SPC. This flexible tool is designed to run locally on the Data Manager or on a third-party remote PC platform, and the exported data

may be sent to one or multiple files. Navigation displays, like the one shown in **4**, allow the user to select data from multiple analyzer platforms – by choosing either unit procedure, equipment, analyzer channel or data tag – across one or multiple production batches. Additionally it is possible to extract different parcels of data by selecting different time slices.

Still much to do

Although still in its infancy, many of the benefits of PAT can be seen as new techniques and analyzers are developed. However, if the full benefits of the FDA initiative for PAT are to be realized, recognition by many existing roles (QC, automation, validation, etc.) is required together with the appropriate training and the ability to identify opportunities for using PAT in their processes. ABB's engineering services for PAT support users in these areas, along with validation, regulatory compliance and other business improvement consultative services. In any case, a standardized global approach is still needed. System suppliers must help to create this standardization, especially in key areas such as data handling. In addition, a solution is needed to break down the barriers created by multiple disparate systems. ABB is such a supplier and ABB's IIT for PAT is such a solution.

4 A typical data selection screenshot from the PAT Data Export Tool



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Footnote

⁴ These may vary depending on the analyzer type but not between analyzer products. In other words, an NIR (Near Infrared) faceplate is the same for both an ABB and Bruker NIR analyzer.

Further reading

Roy, J., "Process Analytical Technology," *ABB Review Special Report on Instrumentation and Analytics*, 2006, 61–64.