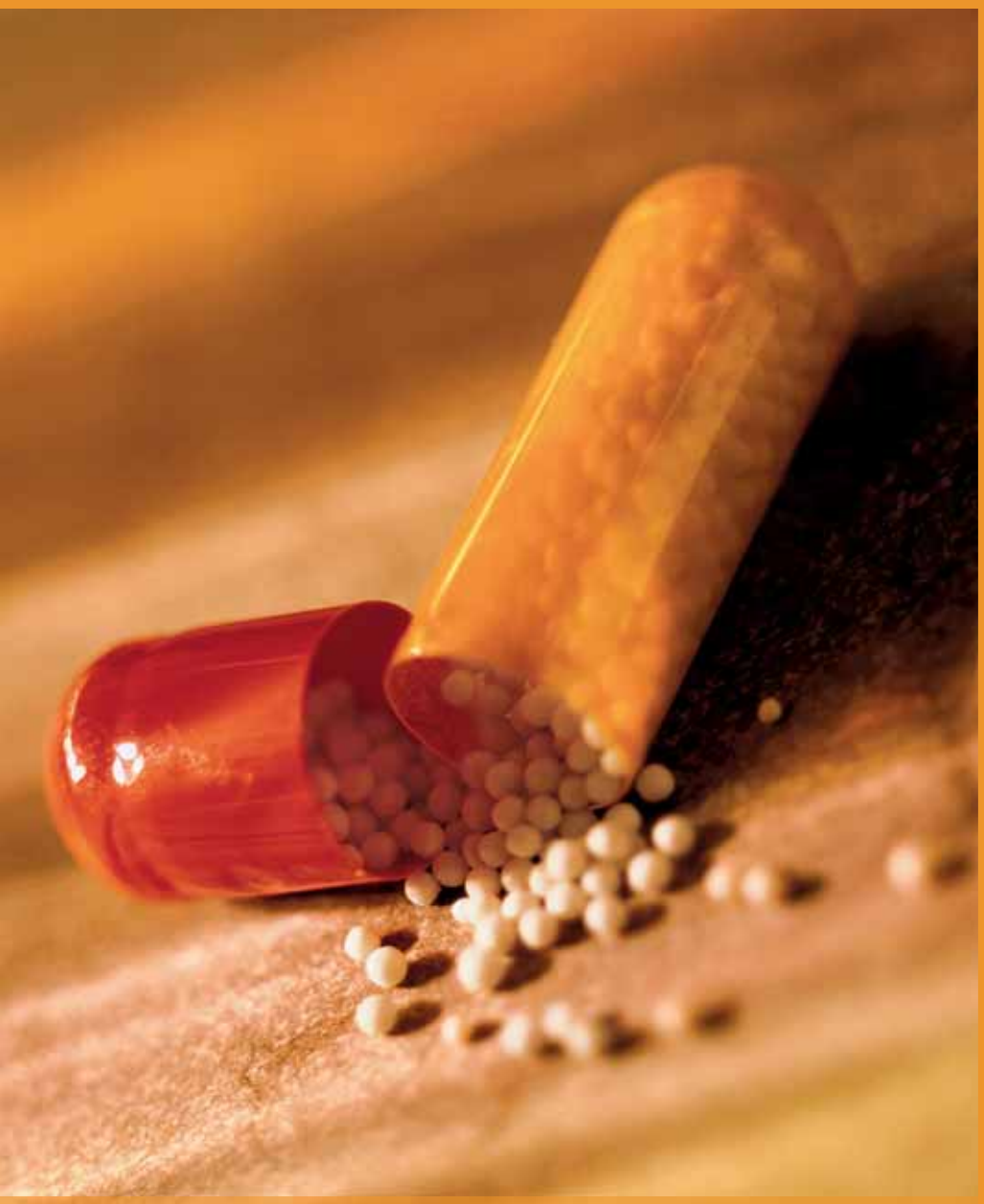
Process Analytical Technology

Integrated PAT solutions for the Life Sciences industry

Thomas Buijs



Pharmaceutical manufacturers have been providing medicines for more than 60 years using tried and tested formulations and manufacturing and quality management processes. In recent years new innovations in measurement, control and IT technologies have helped them to manage their processes more efficiently, with higher productivity as a result.

In addition to these innovations, a specific initiative has also been making its presence felt. Known as the Process Analytical Technology (PAT) Initiative, its goal is to understand and better control the entire manufacturing process within the pharmaceutical industry. Processes are actively managed to achieve a high degree of repeatability and efficiency, and quality assurance becomes continuous and real-time activity.

ABB is working in partnership with its customers to deliver a systems approach to PAT. From measurements to process improvement, ABB supports PAT implementation and the delivery of real business benefits.

Process Analytical Technology (PAT) is a system for designing, analyzing, and controlling manufacturing processes based on an understanding of the scientific and engineering principals involved, and identification of the variables which affect product quality. The PAT initiative is based on the FDA (The US Food and Drug Administration) belief that: "quality cannot be tested into products; it should be built-in or should be by design."

The primary goal of PAT is to provide processes which consistently generate products of a predetermined quality. Effective PAT implementation is founded on detailed, science-based understanding of the chemical and mechanical properties of all elements of the proposed drug product. In order to design a process that provides a consistent product, the chemical, physical, and biopharmaceutical characteristics of the drug and other components of the drug product must be determined.

The role of on-line advanced measurement systems is pivotal to realizing the benefits of PAT. However, the transformation of process performance to provide greater efficiency and cost effectiveness, in addition to assured quality, requires much more than the application of measurement technologies.

Realizing such gains also requires an integrated measurement, control, workflow management and information environment which meets the needs of research and development, manufacturing and quality processes within the business.

Using PAT, ABB offers a unique industrial solution so that its customers in the Life Sciences industry can enhance their processes to deliver the benefits of PAT, from process investigation right through to achieving operational excellence.

The benefits of PAT

In a nutshell, the benefits of PAT can be summed up in the following sentences: PAT improves asset uptime and availability for pharmaceutical unit operations by up to 40 percent. Costs are reduced by up to 30 percent while fundamental product quality is maintained. How this is achieved is outlined in the following paragraphs.

Better process understanding

The physical and chemical processes involved in the manufacture of pharmaceuticals are complex and not well understood. However, during both the development and manufacturing stages, PAT-enabled processes provide access to information rich data – in real-time – which can be "mined" to find the critical quality parameters through multivariate analysis. Once these are determined, it is then easier to establish accurate control schemes for the relevant process parameters so that a more robust process can be established in a shorter timeframe and right-first time production is ensured.

Repeatable batch trajectory

Quality control requires a highly detailed level of process understanding. ABB offers a combination of advanced and regulatory control based on robust process models that deliver verifiable results. The PAT solutions detect and manage critical control points in the process so that deviations from a required profile are correctly managed and fed back into the high performance control zone.

Reduction in overall cycle time

Processing to a quality-based endpoint is a key part of the PAT quality assurance regime. This eliminates wasted cycle time associated with processing using a fixed time-based endpoint including subsequent reprocessing time – and provides a streamlined workflow through the facility.

Reduction in Quality Assurance (QA) costs

Reduction in Out of Specification (OOS) events and consequent investigation leads to significant cost savings. PAT enabled unit operations reduce the reliance on laboratory testing and associated lead times, thus reducing the overhead costs associated with product quality.

Improvement in Overall Equipment Effectiveness (OEE)

OEE is the industry accepted tool to measure and monitor production performance. It can be applied at the machine, manufacturing cell or plant process level. Making cycle times repeatable and reducing in-batch down-time through improved control and early fault detection delivers a more flexible agile asset with much improved OEE.

ABB's PAT Center of Excellence (CoE)

Following the need to offer an integrated approach to PAT, ABB created a CoE in 2004. Its mandate is to develop ABB products and services which will enable customers to reap the benefits of PAT. The PAT CoE builds on ABB Analytical's experience of providing Pharmaceutical PAT Fourier Transform Infrared[1)] (FTIR) and Fourier Transform Near Infrared (FT-NIR) analyzers to the market for the past ten years, as well as ABB's position as a leader in Automation and Control, in particular with its 800xA platform.

The PAT CoE leverages ABB's global resources, which include experienced research and development personnel, application specialists, chemometricians, process engineers, IT engineers, senior validation consultants and advanced process control specialists. Its mandate covers the entire range of PAT applications:

- Initial integration with Manufacturing Excellence programs
- Multivariate analysis
- Basic and advanced analyzers
- Data gathering
- Data storage
- Data mining
- System integration
- Connectivity with manufacturing and business systems
- Advanced Process Control (APC)

Analytical and measurement technologies – the platform for PAT

At the heart of any PAT system is a series of measurements made on real processes under realistic manufacturing conditions. Data from conventional process measurement systems (eg, temperature, pressure and flow) give some insight into manufacturing processes so as to achieve a basic level of process understanding. However, manufacturing processes are usually too complex for simple approaches to be effective in achieving process understanding and control. An in depth degree of understanding and tight con-

Footnote

1) See also "Waves to data", ABB Review 3/2006 pp 73–74.

trol can only be achieved by employing the correct technologies to measure relevant process parame-ters. These technologies are often based on chemical composition and/or physical form measurements, ie analytical techniques.

ABB has top class analytical technologies, from FT-IR/NIR spectroscopy right through to mass spectrometry and Gas chromatographs. Fully integrated into ABB's Industrial IT (IIT) concepts, the systems have unparalleled connectivity capability and provide a robust measurement platform for all PAT applications. Connected to the IIT information backbone, the process data developed can be used in everything from advanced control to process troubleshooting.

FT-IR/NIR analytical solutions

FT-NIR is, by far, the most widely used and proven analytical technology for PAT applications. ABB has ten years of experience in supplying off-line, at-line and on-line FT-IR/NIR PAT solutions to the pharmaceutical industry and is a preferred supplier of most of the leading companies. Turn-key analytical solutions are provided for research and development for scale-up, drug substance, and drug product manufacturing.

Typical drug substance solutions include:
- Reaction monitoring
- Fermentation monitoring
- Crystallization monitoring
- Dryer monitoring
- Solvent Recovery monitoring

Typical drug product applications are:
- Raw material identification
- Blend monitoring
- Spray coating monitoring
- Fluid bad dryer monitoring
- Solid dosage form content uniformity
- Moisture in lyophilized solids

Even though the available analytical technology fulfills a wide variety of measurement needs, there is still a very wide Information Technology gap which is preventing the industry from efficiently gathering and using this data in real-time for process understanding and control. To be more specific, most of the advanced PAT analyzers currently available do not share a common user interface and data format, and do not offer the connectivity required to efficiently exchange this data with plant and business systems. Furthermore, the data is highly scattered and is not available in real-time in a central location.

The Industrial^{IT} for Process Analytical Technology suite

To address these drawbacks, ABB is currently developing an Industrial^{IT} PAT suite that features an integrated IT platform using proven analytical and automa-tion core components. This platform is based on the award winning 800xA Industrial IT Automation technology[2)]. The concept 1 is based around a flexible, modular, scaleable and open architecture 2 which uses OPC – a standard communication protocol – to exchange data between modules.

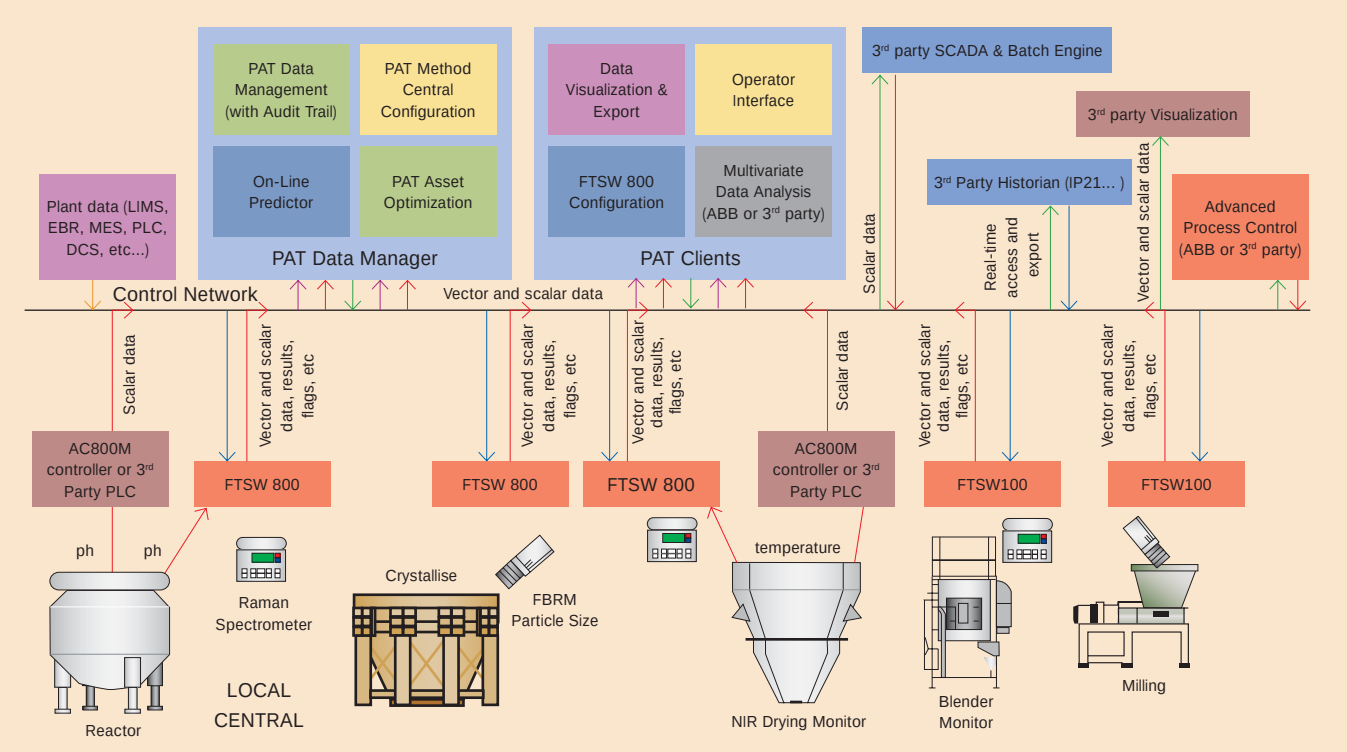
FTSW800 – Analyzer control process software for data acquisition

This flexible, open architecture process analyzer software 3 is designed for implementing analytical methods and control sequences. It offers a single platform for the local control of multiple analyzers from spectroscopy (IR, UV-VIS, Raman etc) to other advanced analyzer types (particle size, acoustics, HPLG, mass spectroscopy etc). In addition, it provides unified engineering and

Footnote

[2)] http://www.abb.com/productguide Information on ABB's 800xA Industrial^{IT} Automation technology is found under the "Control Systems" section.

1 Industrial^{IT} for PAT concept



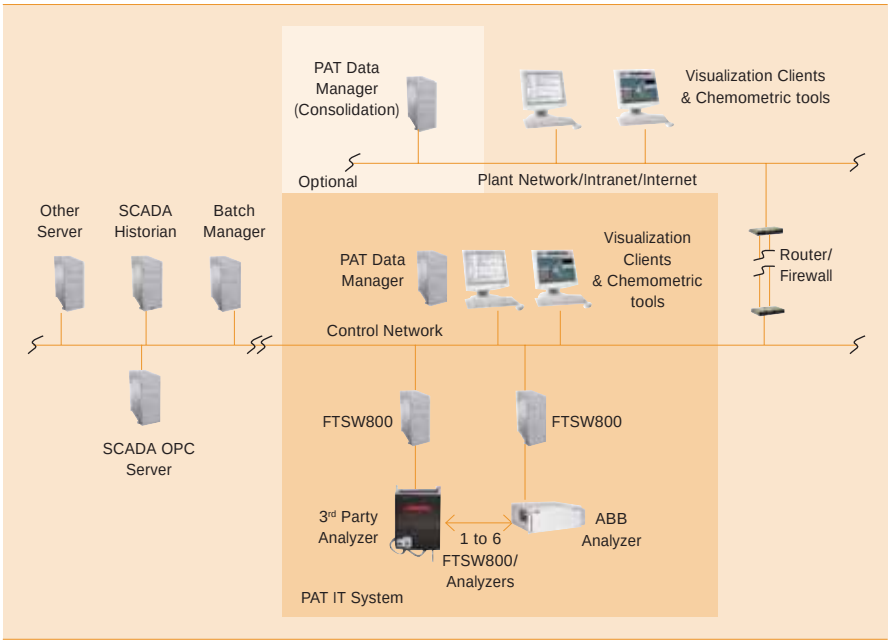
operator interfaces as well as tools for multivariate analysis and predictions.

Data storage: PAT data manager

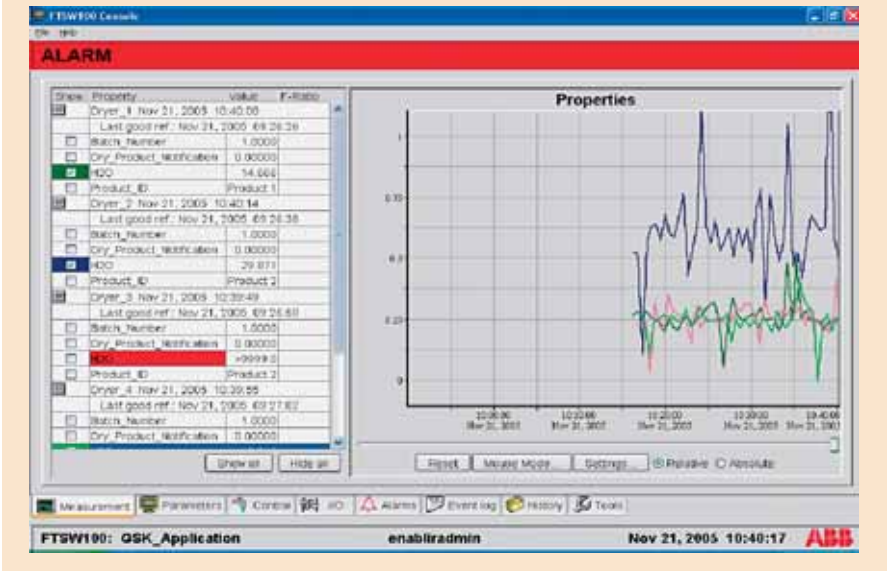
The management of PAT data is highly complex not only because the flow of information is enormous, but because it also includes a mix of data formats (spectral, vector and scalar data) that makes it difficult for standard historians to handle. Furthermore, the centralization of PAT data is not sufficient as it needs to be combined with the batch information coming from the process control system (PCS) and the business systems.

ABB's PAT data manager is unique in that it stores all the data in a single distributed database and can handle huge flows of both scalar and vector data coming from the analyzers, the PCS and SCADA systems: It handles the batch structure data, the vector and scalar data, alarms and events as well as a complete audit trail. It can also exchange data with other third party historians

2 Industrial^{IT} for PAT network architecture



3 Local trending with FTSW800 software



Data mining, visualization, multivariate analysis, and batch Management

The Industrial^{IT} for PAT suite includes a wide range of modules to provide an operator workplace, central method configuration, multivariate analysis batch configuration and management as well as asset management for analytical and process equipment. The system also has the ability to connect to third party commercial multivariate analysis tools for off-line and real-time predictions.

Control

Controlling processes in a flexible and repeatable manner requires process understanding to be realized within regulatory and advanced control environments, while at the same time taking advantage of a range of process models. This is facilitated by dynamic solutions – predict, control and inferential measurement platforms which integrate with operator interface, and regulatory control and process data management components.

The way forward

PAT provides an opportunity to move from the current "testing to document quality" paradigm to a "continuous quality assurance" paradigm that can improve a company's ability to ensure that quality has been "built-in" or is "by design". Not only that, but it gives companies a greater insight and understanding of their processes; it provides the potential for significant reduction in production (and development) cycle times; and it minimizes the risk of poor process quality.

PAT will revolutionize the way pharmaceuticals are made and will forever change the face of the industry. This is why ABB's investment in PAT is the single biggest development initiative in Life Sciences, and it also presents the company with an exceptional opportunity to become the market leader in Life Sciences.

Thomas Buijs
ABB Automation Technology
Process Automation
Quebec, Canada
thomas.l.buijs@ca.abb.com