Process analytical technologies: a unique data management challenge

synTQ v4.0

Optimal industrial automation

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Management Briefing

Encouraged by the FDA, life science industries around the world are adopting Process Analytical Technologies (PAT) to improve the quality, reliability and cost-effectiveness of their manufacturing processes. Theoretically, PAT has the potential to revolutionise pharma manufacturing, by compensating for input variability, tightening finished product specifications, cutting production cycle times and, ultimately, enabling the real-time release of products to market.

Before they start to reap those benefits, however, companies need to master a broad set of new capabilities and new technologies, and to develop the processes to integrate those skills into their product development and manufacturing operations. A successful PAT implementation demands the ability to deploy a range of sophisticated analytical equipment, including but not limited to Near Infrared, (NIR), Fourier Transform Infrared (FTIR) and Ramen. It calls for advanced chemo metric modelling capabilities to enable the prediction of your product Critical to Quality Attributes (CQAs) in real time from the spectral data sources. It requires an unprecedented level of process understanding, to determine exactly how your Critical Process Parameters (CPPs) affect your process and why they affect your process in that way (i.e. mechanistic understanding), and it needs the process control capabilities to implement effective feedback or feed forward loops in manufacturing by controlling your Critical Control Parameters (CCPs).

On top of all the skills required in a deployment, PAT also presents a data management challenge that is unlike anything else experienced today, in the pharma sector or elsewhere. In this article, we look at the nature and scale of that challenge, and make the case for the adoption of dedicated data management technology as a key enabler for reliable, regulatory compliant and economically viable PAT implementations.

Market leader release white paper on data management solutions for pharmaceutical manufacturing ‘Process analytical technologies: a unique data management challenge’

Process analytical technologies (PAT) have the potential to revolutionise pharma manufacturing, by compensating for input variability, tightening finished product specifications, cutting production cycle times and, ultimately, enabling the real-time release of products to market.

Successful PAT implementation requires companies to master a broad set of new capabilities and new technologies, and to develop the processes to integrate those skills into their product development and manufacturing operations.

> *“PAT presents a data management challenge that is unlike anything experienced today, in the pharma sector or elsewhere.”* - Author, Martin Gadsby, MD Optimal.

This challenge arises from three basic characteristics of PAT implementations: analytical datasets that are large, complex and difficult to collect; the requirement for complete traceability and comprehensive records of collected and derived data, models and process parameters; and the commercial imperative for commercial considerations call for fast, reliable development of PAT methods, and rapid manufacturing ramp-up.

This paper form Optimal looks in detail at each of these requirements, and makes the case for the use of a dedicated PAT implementation software environment (Optimal synTQ®) to provide a unified framework for data collection, model development, process control and continuous improvement.

Why PAT data management is challenging

The data management challenge in PAT arises from three basic characteristics of PAT implementations. First, the nature of the measurement equipment and models used mean that analytical datasets are large, complex and often difficult to synchronise and collect. Second, the highly regulated nature of the pharmaceutical manufacturing environment requires complete traceability and comprehensive records of collected and derived data, models and process parameters. And third, commercial considerations call for fast deployments of PAT that deliver a high quality product with a truly realised ROI. This in turn necessitates the rapid development of reliable PAT methods and models, the quick determination of the process mechanistic and the speedy development of control models. Let's examine each of these three characteristics in turn.

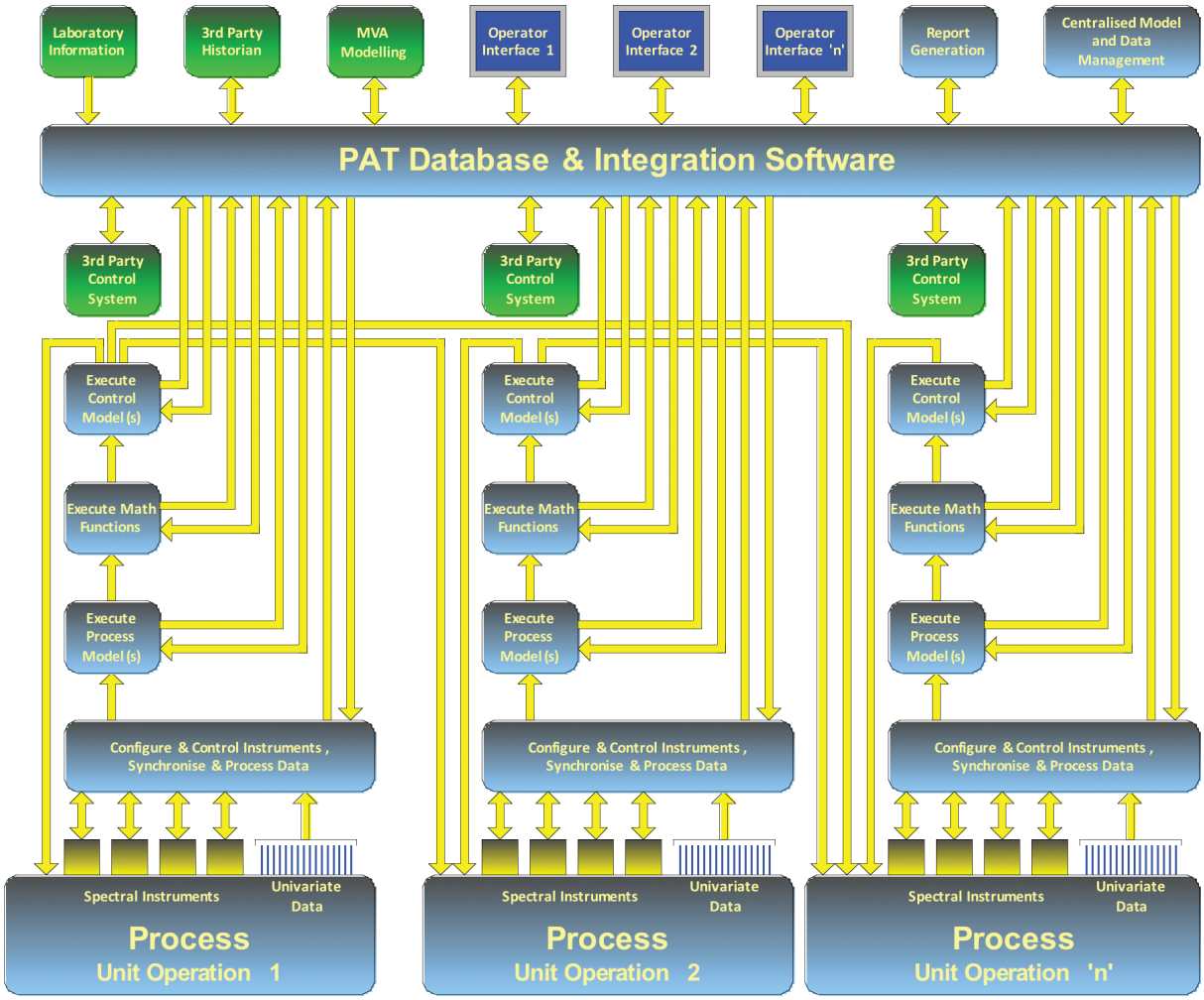
Data complexity

Data collection for PAT in the pharmaceutical environment relies heavily on instruments that produce spectral results. Such instruments don't simply create larger data sets than single-parameter instruments (temperature, pressure etc.), the collection of useful data also depends on the calibration and referencing status of each instrument, the settings used during operation and any spectral manipulations carried out on the data at the time of acquisition.

That complexity is compounded by the need to integrate and synchronise data from multiple instruments and measurement technologies, including at-line, on-line and in-line instruments plus univariate data sources.

Due to the various instrument scan speeds and data collection rates the synchronisation of the data acquisitions can be complex and necessitate the triggering of instrument read requests at specific times in order for the data set to be valid and representative of a specific material sample. Furthermore, during the model building and continuous improvement exercises there will be the requirement to associate the CQA results of samples obtained from off-line analysis of with specific analytical data sets. This data association requirement will continue through the process understanding phase and indeed for the whole lifecycle of the product in the form of continuous improvement.

As companies go on to build their process models using the data manager and chemetrics modelling there is additional complexity: picking subsets of the recorded data or selecting particular runs, discarding unwanted data and manipulating the remaining data sets to suit the requirements of their models.



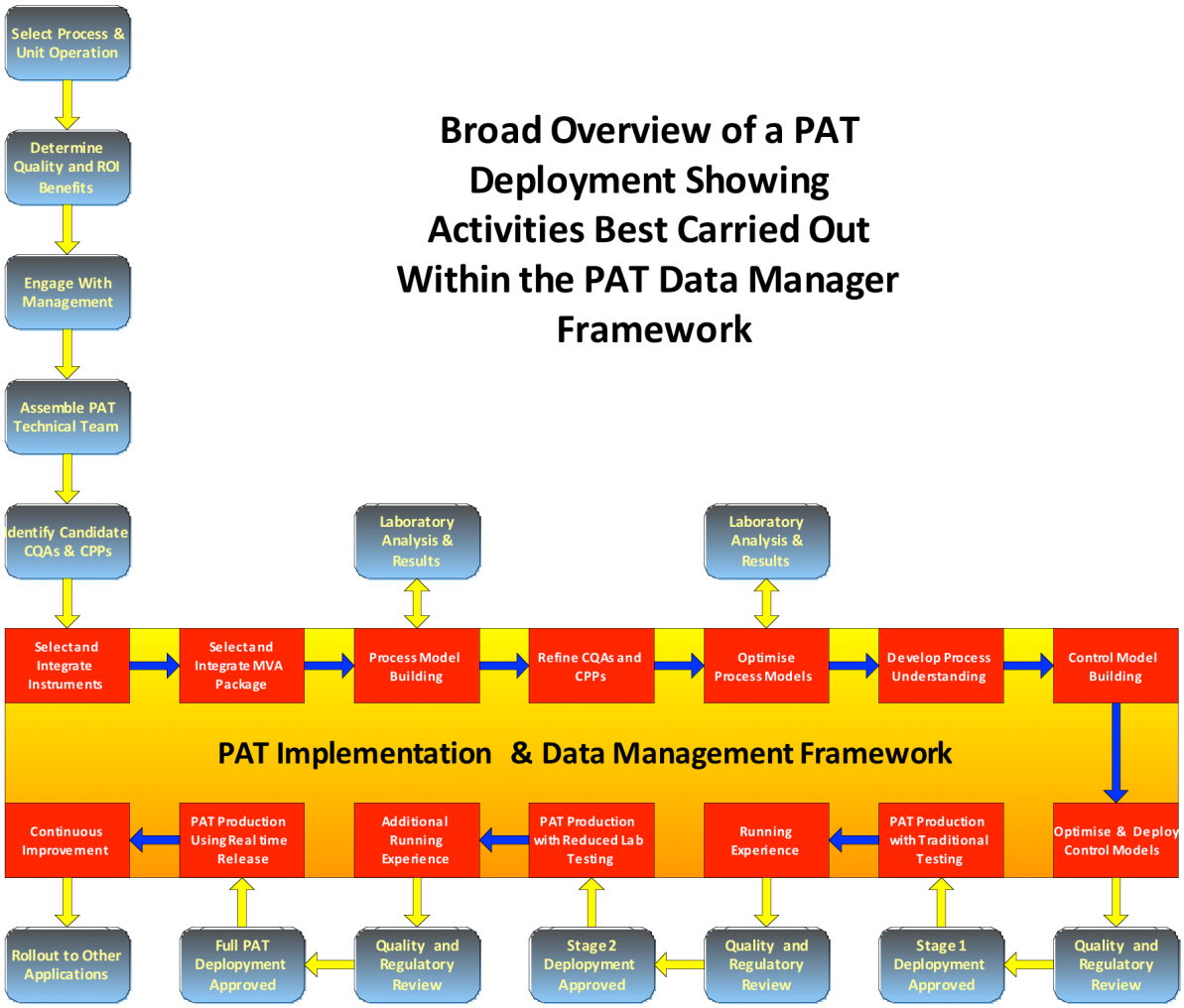
Regulatory requirements

Pharmaceutical manufacturing is one of the most tightly-regulated business environments in the world. Manufacturers must retain comprehensive records of batch and process data (with real time release data being critical), an auditable trail of the control parameters, plus a full and detailed life history of all the models used in each process.

They must ensure that the software they use to manipulate data, run models and control process equipment performs in a regulatory compliant manner too. During development, they must be able to test alternative models and control approaches, and during production introduce continuous improvements in a compliant manner. As companies increasingly adopt distributed production models and extended supply chains, they must be confident that meticulous record keeping and tight control over process technologies is retained for the full lifecycle of all products.

The productivity imperative

The complexity and regulatory compliance challenges of PAT can be overcome through rigorous record-keeping, care in data manipulation and analysis and the creation and testing of dedicated custom software. But “manual” methods like these have some critical limitations in a commercial PAT implementation sequence. They require the scientists and process engineers in charge to spend more of their time on non-value adding functions, like record keeping, data manipulation and error checking, and less on the important work of running experiments and building and refining models. Also the software that has to be developed is project specific, difficult to develop and validate, takes a great deal of time and is expensive. These inefficiencies lead to a direct trade-off between the quality of the PAT implementation, its cost and the time taken to develop it, and acts as a disincentive to further refinement and continuous improvement once a process is performing acceptably but not optimally.



PAT implementation management

The need to address these challenges has led to the development of dedicated PAT implementation management software, of which our own synTQ® system is an example. PAT implementation managers are designed to provide a unified framework for data collection, model development, process understanding exploration, process control development and continuous improvement, all in a regulatory compliant framework.

Their objective is to simplify, automate and accelerate PAT processes wherever possible and to provide a seamless environment for the development of PAT methods from the laboratory through to distributed global manufacturing environments. Using our own offering as an example, let's examine the way an implementation manager works through the complete PAT development process.

In the development laboratory

As companies begin to develop their initial chemo metric models, synTQ® can operate as a laboratory data manager for raw material identification and characterisation, for small initial research experiments or for process development experiments on pilot scale equipment. synTQ® can interface with a broad range of third party analytical instruments to set and ensure their configurations, to trigger measurements as necessary and store results, all data naturally being time stamped and all important operator actions stored in an audit trail. As in a production environment, using a PAT implementation manager in this environment allows the synchronous operation of instruments and collection of univatiate data as necessary to allow the building of MVA models using compound information. The system also interfaces with standard laboratory information management systems (LIMS), allowing results obtained from samples analysed in a laboratory to be stored in the synTQ® environment and quickly associated with the relevant spectral data gathered in real time.

The ability to quickly and automatically set instrumentation based on previously established settings, modifying parameters where necessary with all critical data being automatically recorded, helps researchers to rapidly and reliably conduct multiple experimental runs as they assemble the data they need to support the development of product specific process models.

Process model development

During the process model building phase, synTQ® provides integrated access to all measured data, with a graphical user interface that allows quick visualisation of recorded data, rapid selection of the most appropriate datasets to feed the model and the simple exclusion of unwanted results. Once again, the selections and data manipulations made are all recorded, allowing additional or alternative datasets to be loaded into the model with ease.

This automated data manipulation process is one of the key drivers of improved productivity in early stage PAT development, and some users have found that the approach reduces the time taken to prepare data for input into a model from several hours to a few minutes.

The ability of a good PAT implementation manager goes even further in the model development phase. Companies, can for example, test the performance of models using historic data that has not been used in the model building process, and test multiple versions of models at the same time, these techniques dramatically reducing the number of experiments needed to optimise a model this of course saving significant time and money. This multiple model testing capability can even be executed on models from different vendors, this being especially important if a client needs to migrate their models from one vendor to another. Moving more model development and testing activity from a sequential to a parallel activity like this has significant potential to accelerate the whole model development process.

Developing process understanding

Process understanding is a key imperative of a PAT implementation, and this must be gained in a cost effective and timely way. To do this you will need to not only run your Design of Experiments (DoE), but do so in an environment that is information rich, allowing the user to gain process relationship insights in real time as well as on historic data. A good PAT implementation manager delivers on both counts. For example, with synTQ® you can view all the data in real time, and immediately see the effects on the process, CQAs, CPPs and other selected data values when an input CCP is changed. This real time view has huge time saving impacts; however all the historic data will of course be available retrospectively for viewing and reporting on in a myriad of ways.

Control model development

Armed with your process models and process understanding, the next step is to develop the control models, these being used to close the loop using either feed-back or feed-forward control to ensure that the quality of your product is optimised and production time is minimised. Again by using synTQ® as an example, control models can be either within synTQ® (in the form of MatLab®) else via your preferred control system – typically but not essentially a PLC or DCS. Due to the personnel involved in PAT deployments, it is often more time and cost effective to create the development control models in Matlab®, as the same staff who has to date been working on the system are normally conversant with this technology. MatLab® would run within the synTQ® environment, and as with MVA models, you can test more than one control model at the same time although you can obviously close the loop using only one. As with process model development, the ability to study the performance of more than one control model at the same time and in real time can greatly speed up this activity. When the model is fit for purpose then it can either be used as –is, else the algorithm can be ported to your preferred 3rd party control system.

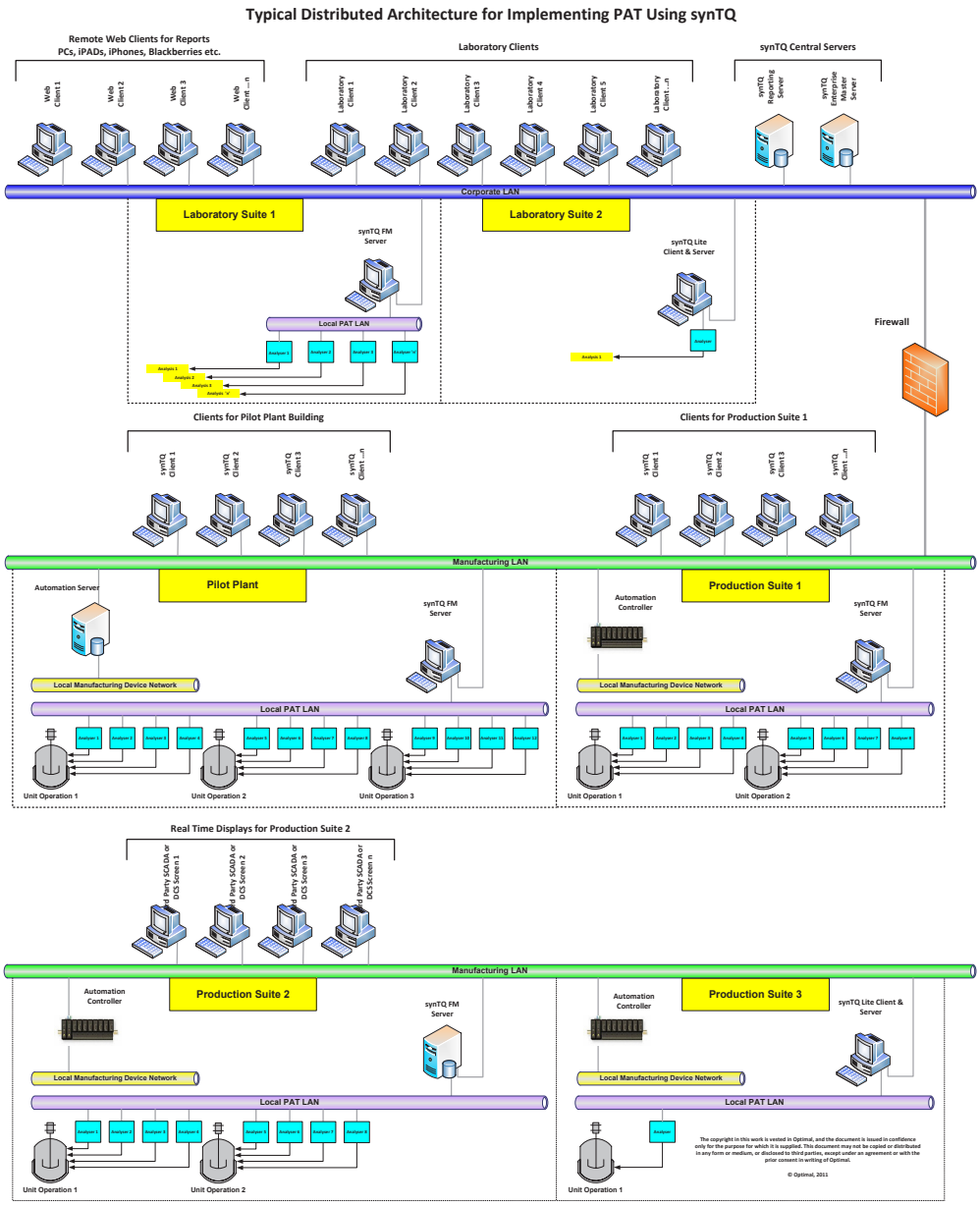
On the production floor

As PAT development moves from the laboratory to the pilot plant, the principals of PAT and the unified framework offered by synTQ® help to further reduce rework and repetition. Where appropriate, instrument settings and measurement sequences can be carried over from the lab, and models developed there can be evaluated and refined using pilot production data. The process understanding that has been gained during the early project stages greatly assist in minimising the scale-up time, this being very significant when it comes to maximising the use of the drug's patent life. And of course the PAT implementation manager will be the vital link between all the instruments, the MVA system and your control system of choice.

When in production synTQ® provides all the necessary views into the process for the operators including (in combination with the MVA package), the ability to provide operators with timely warnings when a process is going outside of its normal operating range. This condition may not be immediately obvious when using traditional univariate data views; however by using simple to understand data that has been derived using sophisticated techniques the provision of such information is possible. This feature can therefore prevent catastrophic system failures that would otherwise result in significant product loss and perhaps equipment outages.

Across the product lifecycle

Once production is up and running, the synTQ® environment allows companies to collect data, run models and operate their processes in a robust and regulatory complaint way. The system can operate seamlessly across local and wide area networks, allowing, for example, the centralised collection and storage of process data from multiple plants, or the central management of PAT methods. The networked structure also allows robust, straightforward report generation from stored data. The same environment allows low risk maintenance and continuous improvement processes, for example, new versions of models can be run off-line in parallel with production models, using real process data in real time to verify their performance before being deployed.



PAT infrastructures can start with a single computer and instrument, but can grow into a distributed Pat Data Management system as shown.

As companies begin to roll out their PAT processes from their laboratories to the global production networks, effective management of instruments, data and models will become a decisive factor in successful and cost effective implementations. Getting that right will require new skills and closer collaboration between functions, but it will also depend on the availability of a reliable, flexible and regulatory compliant PAT data management infrastructure.

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