



# **PRACTICAL GUIDANCE ON HOW TO IMPLEMENT A PAT PROGRAM**

AN AUTOMSOFT WHITEPAPER

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The purpose of this white paper is to deliver a number of key messages relating to Process Analytical Technology (PAT). This is based on our involvement with current and planned PAT implementations as well as discussions we have had with the FDA.

# INTRODUCTION\_

The key points are:

- PAT is here to stay.
- PAT is a philosophy, a new way of manufacturing.
- It will deliver substantial benefits in terms of increased yield and higher product quality.
- It will influence the responsibilities of Manufacturing, Regulatory, Quality and Compliance leadership.
- Data is critical – consolidating all key data for reporting and analysis is the bedrock of a successful PAT implementation.
- RAPID-Pharma from Automsoft is designed to manage all the disparate sources of data and integrate this data into the PAT environment.
- RAPID-Pharma is 21 CFR Part II compliant and provides the required audit trails.
- PAT implementation will not tear the organization apart. It can be implemented in a modular form, with maximum benefits and minimal disruption.
- PAT programs have moved to implementation stage in many of the top ten pharma companies.

Depending on the perspective, the history of the PAT initiative from the FDA varies considerably. The industry has a view, the regulator has a view and the media have a view. However, notwithstanding the historical drivers for PAT as an initiative, certain principles are relevant in understanding the background and rationale for the adoption of PAT by most of the major pharmaceutical manufacturers as well as many of the medium and large biotech companies.

# BACKGROUND

These principles can be summarized as follows:

- (a) A substantial proportion of pharmaceutical production results in batches or output that is 'lost', lower than acceptable yields or not suitable for release.
- (b) The traditional regulatory approval environment instituted a regime of time point-based quality inspection into the process rather than continuous monitoring. The net effect of this regime was approval for drug manufacture being based on a succession of steps in a process. Each of these steps was defined as being performed for a specific period of time.
- (c) This regulatory regime, coupled with the economics of drug development, has resulted in an active disincentive for companies to adopt innovative technology.
- (d) New Process Analytical Technology (PAT) tools such as ultrasound and Near Infra-Red (NIR) can yield continuous measurement during stages of a process and offer the prospect of continuous measurement and improvement during a process.
- (e) Application of PAT to a process enables a move from time-interval based quality inspection to continuous monitoring. This in turn means a shift from a time-based model to an event-based model.

As a result of this set of circumstances, the FDA joined with industry in evaluating PAT as an enabler of increased quality, reduced losses and greater control in the manufacturing process. This was described in the initial FDA guidance document issued in August of 2003 which followed from the description of the new vision of the FDA, 'A Risk-Based Approach to Pharmaceutical cGMPs for the 21st Century' published in 2002.

The final guidance for industry was issued in September 2004 and reflected a number of changes from the original document. They were as follows:

- : Process understanding, acknowledgement of process variability and risk-based understanding are key themes.
- : Biologics are included for the first time.
- : PAT is identified as a philosophy rather than just a technology.
- : Management of variability is emphasized.
- : Continuous improvement and knowledge management are the objective of the guidance.

Perhaps the most significant element in this is the identification of PAT as a philosophy, rather than as a set of instruments or a new measurement technology. Viewing PAT as a way of thinking substantially influences the perspective taken on implementation. However, we also believe that the 'Big Bang' approach to complete PAT-enabling of a manufacturing plant in one step is fraught with difficulty and may act as a deterrent to companies.

So, what issues have been recognized, by industry and regulator alike?

- : It is not necessary to wait for a process to be completed before assessing the quality of the product being manufactured.
- : Measurements collected at different points in the process from different sources are critical to continuous improvement as well as to continuous monitoring. These data sources include PAT instruments, sources of traditional process or continuous data from PLCs and SCADA systems as well as batch and alarm and event data.
- : Massive amounts of data of many different types will be generated, and it must all be consolidated and analyzed together to give a coherent view of the process. Introduction of PAT must not result in the creation of islands of information; otherwise, the benefits will not be realized.

Based on our work to date in the industry, we believe that PAT is here to stay. The current profile of the industry is that there are fewer blockbuster drugs in development, a high percentage of output is discarded for quality issues (figures of between 20% and 40% of total output have been put forward by analysts) and manufacturing costs are an issue. PAT is a program that addresses the aligned needs of the industry and of the FDA, namely, lower cost of manufacture, higher quality and control, and consistency in process and output.

# HOW PAT IS EVOLVING - THE AUTOMSOFT VIEW

What we have observed since the publication of our first white paper on this topic over a year ago has been the enthusiasm with which most of the larger companies have embraced PAT. They have challenged their software providers as to their PAT strategy, created their own strategy and have engaged with colleagues in the industry and with regulators. This has encouraged thinking and created an understanding of the practical benefits of the new philosophy. There is a clear recognition that PAT enables the innovation that the industry badly needs and that the FDA and the industry are partners in driving its adoption. At least eight of the top ten global pharma companies have initiated their own PAT projects. These projects have moved from the initial analysis stage to planning and implementation of PAT in limited phased stages as part of an overall strategy to drive the benefits with minimal disruption.

## EARLY STAGE PAT IMPLEMENTATION

Early stage PAT implementations involve the review of processes to identify the potential application of a PAT 'module' and the subsequent installation to eliminate or minimize losses associated with an identified risk in the process. Take a process as described in Figure 1. The individual steps are undertaken for a defined time period, managed by the control system. All of the process data is collected and stored in a data historian or process database. This enables post-process analysis, as well as storage of batch process data to comply with 21 CFR Part 11 and other regulatory requirements. This is a typical technology structure prior to implementation of PAT. In this particular case, each step in the process: dispensing, blending and compression, is performed for a specific period of time, regardless of the outcome. The result is that if there is any variability in the input ingredients then there will be variability in the outputs.

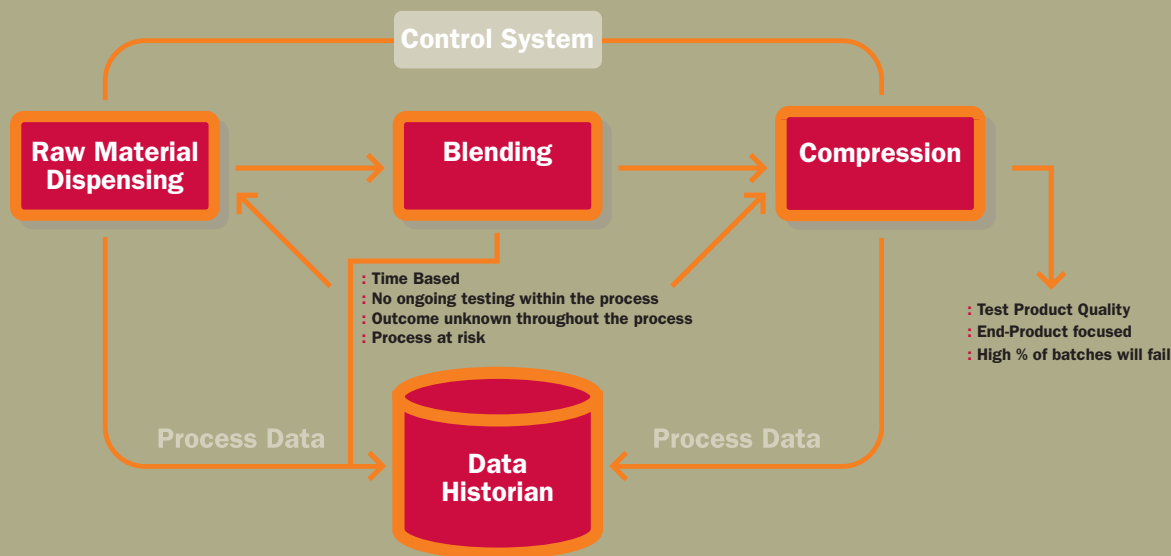


Figure 1.

# HOW PAT IS EVOLVING - THE AUTOMSOFT VIEW

Following a review of the process in this example, it is determined that the majority of variability occurs in the blending stage. Based on the size of the granules in the ingredients, the time specified for blending may be too short but at other times correct. In Figure 2 below, a PAT device has been introduced into the blender. This device is a Near Infra-Red (NIR) instrument which is attached to a workstation. The instrument, in this case, stores an NIR 'picture' of a fully blended batch. When the blending operation starts, the instrument takes continuous NIR pictures of the batch and compares them to the complete or model picture. When there is a match, it sends a signal to the control system to tell it that blending is now complete. This means that the stage in the process continues until complete, rather than for a defined time period. Variability in inputs is offset by ability to vary the blending time by a continuous assessment and control technology.

## THE DATA MANAGEMENT ISSUE

However, one impact of the introduction of a PAT instrument is that we now have data associated with the batch stored in two different locations: one for process data and the other, the PAT instrument workstation which stores the NIR images or spectral data. This early-stage PAT approach has the advantage of applying the technology in an immediate fashion to a key point of risk in the process and addressing this risk.

However, it also has the effect of creating an island of information, of PAT data. This introduces a control risk into the process in that data associated with the batch is held in two locations with implications for Part 11 compliance. It also creates a significant manual overhead to associate the PAT data for the batch with the process data for the batch in order to produce a complete picture for continuous improvement.

Why is it necessary to have all the data in one place? There are three critical reasons:

- : A separate location for different types of data associated with the process introduces compliance risk.
- : A single store is necessary to ensure all the data is available for analysis.
- : Data associated with the process cannot be viewed in isolation to infer product quality. For multivariate data analysis to occur, the PAT and the process data must be analyzed together to evaluate interaction between different measures at different points in the process. Multivariate data analysis is a core component of a PAT strategy and is identified as such by the FDA.

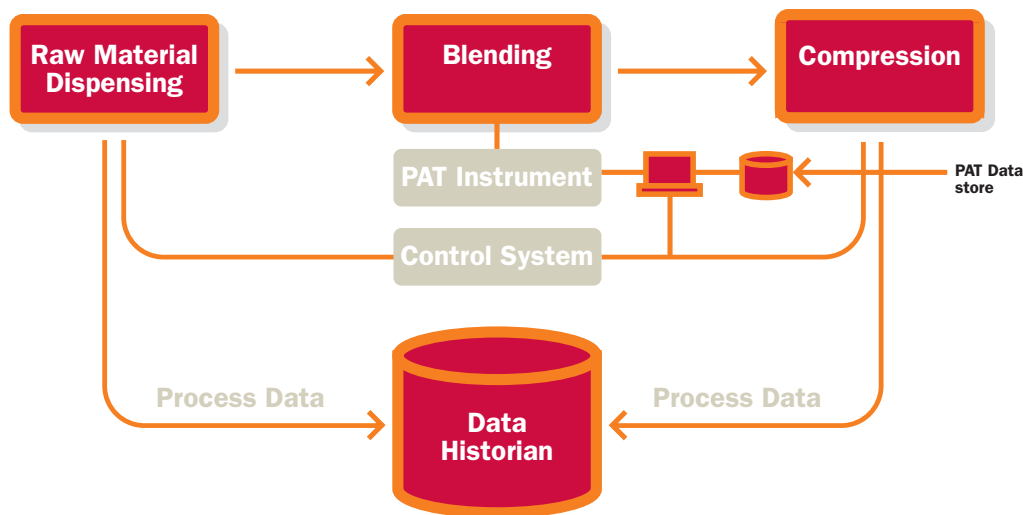


Figure 2.

# HOW PAT IS EVOLVING - THE AUTOMSOFT VIEW

The solution to the data management challenge is to address PAT from a strategic perspective, working from a structured methodology. Recognizing at the outset the critical nature of data management, the solution should look similar to **Figure 3**. This has the advantage of enabling collection, storage and analysis of all the data in one place. It also ensures compliance with Part 11 and allows more PAT devices to be added to the existing infrastructure with minimal disruption and in a modular fashion. RAPID-Pharma is a data management solution specifically designed to address all manufacturing data management challenges, addressing not only PAT but also analysis and reporting, Part 11 and process data storage.

## RAPID-PHARMA: A FUNDAMENTAL COMPONENT OF A SUCCESSFUL PAT PROGRAM

This section examines, in more detail, the data and batch record management issues facing those considering a PAT deployment. In particular, it describes the volume of data generated in a PAT environment and the difficulties involved in managing and accessing this data. The Automsoft solution to PAT data management is presented as a flexible, scalable database and reporting system which addresses these challenges.

## THE DATA MOUNTAIN

As PAT implementations generate several orders of magnitude more data than a traditional pharma manufacturing operation, management of this data is clearly problematic. In non-FDA regulated industries, this was less of a burden as once the smart instruments were calibrated and the appropriate models were in place, the raw and derived data from such instruments could be discarded. In other words, only high-level summary data passed to the control system needed to be retained for reporting and analysis requirements. In this scenario, raw and derived data can be generated and stored on demand to tune the instrumentation or for recalibration. Most instruments simply emit a stream of binary data as a series of files, which are then stored in a computer file system.

However, in the case of FDA regulated environments, the approach to data storage is different. In keeping with other FDA data retention policies, at a minimum, all of the derived data must be stored and made available to the agency if required. This presents a challenge to existing database systems and historians which are not designed to interface with the instrumentation nor manage these mountains of binary files.

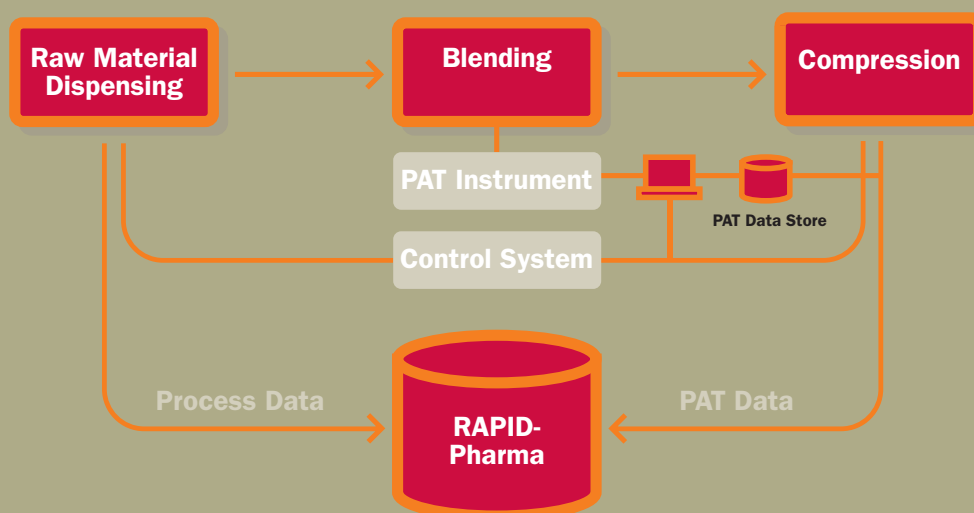


Figure 3.

# HOW PAT IS EVOLVING - THE AUTOMSOFT VIEW

## BATCH RECORDS

A further challenge in PAT is how to report on the data from across the process. Again, the final guidance from the agency is very vague in this area (although the ASTM committee E55 is expected to address this issue with a series of standards documents. See [www.astm.org](http://www.astm.org) for further information<sup>1</sup>). This challenge involves making two important decisions: deciding what should be included in the batch record for a PAT process and deciding what should be reported on. It is unlikely that raw data would need to be incorporated in a report or the batch record. However, as today's data management systems are not designed to associate PAT models or derived (PCA) data with the 'traditional' continuous, alarm and batch data, any solution in this area will be specific to each implementation and inherently inflexible.

## RAPID-PHARMA

The technical barriers described above are due to the lack of a standard software infrastructure to manage all of the data generated by a PAT manufacturing process. This barrier has been eliminated with the rise of next generation software systems such as RAPID-Pharma from Automsoft.

RAPID-Pharma has been designed as a distributed data management system which can capture, warehouse and report on PAT data together with more typical data from PLC, DCS and SCADA, all in a secure 21 CFR Part 11 environment.

## CAPACITY

The system has been designed to cope with very large volumes of data, such as high frequency spectra from NIR devices, and can also warehouse 'traditional' process data from SCADA and DCS, all in one central secure database.

This database system has been designed from the ground up, to efficiently collect, store and serve:

- : binary data (PAT models, raw spectra, SPC and PCA files)
- : continuous data
- : alarm and event data
- : batch (S88) data

## INTERFACE

PAT data is collected directly from the instrument workstation (or from where it resides). Automsoft is working closely with leading instrumentation vendors to support this effort. Data from other systems is typically collected via the industry standard OPC family of protocols.

## ARCHITECTURE

The distributed architecture of RAPID-Pharma allows for multiple production lines and PAT instruments to be concentrated into a single RAPID-Pharma system. Data from across the plant or facility can then be reported on. This architecture, coupled with virtually unlimited data storage<sup>2</sup>, means that RAPID-Pharma can manage many years of data online, including years of raw spectra if required.

## REPORTING

RAPID-Pharma includes a set of powerful web-based reporting tools. These tools may be used by anyone familiar with a web browser and allow for ad hoc and complex predefined reports. The tools are 'PAT aware' and both PAT and process data may be combined in a single report.

<sup>1</sup> Automsoft is a member of the E55.02 committee and is working on WK5931 – Standard Practice for PAT Data Management

<sup>2</sup> Capacity is limited only by physical storage. TB range RAPID-Pharma systems are not uncommon

Implementing PAT as a strategic direction, as described above, requires a planned, disciplined approach and a strategic rather than a tactical view. It is this strategic view that avoids creating new islands of data and instead addresses each of the integration challenges as part of a philosophy.

# IMPLEMENTATION METHODOLOGY

To adopt PAT, it is essential to utilize a methodology which achieves a number of objectives, namely:

- : Identify the opportunities for greatest return.
- : Understand the existing process at a detailed level prior to change, to ensure that any change has minimal disruption and has a clear quantified benefit over the previous process.
- : Ensure that any program is part of an overall strategy which has as its objectives, an improvement in quality, reduction of cost and elimination of compliance issues.

Figure 4 below, proposed by John Davis of Lloyd’s Register Serentec, Inc. is a sample iterative methodology which enables all of the above objectives as well as ensuring that there is a clear and solid process for continuous improvement.

## STAGE 1 – DISCOVERY

The Discovery stage is the initial analysis and evaluation stage of the project. The tasks undertaken at this stage are:

- : Identify and establish the team.
- : Analyze the processes to identify those which will benefit from PAT.
- : Identify critical control points and quality attributes.
- : Explore potential PAT opportunities.
- : Create PAT project plan.

At the end of the Discovery stage, there should be a multi-disciplined team in place, fully co-ordinated in terms of the objective of the project. There should be a detailed process map, with associated critical points and measures identified. This should drive the initial identification of PAT opportunities which provides input for the creation of a project plan for the entire project.

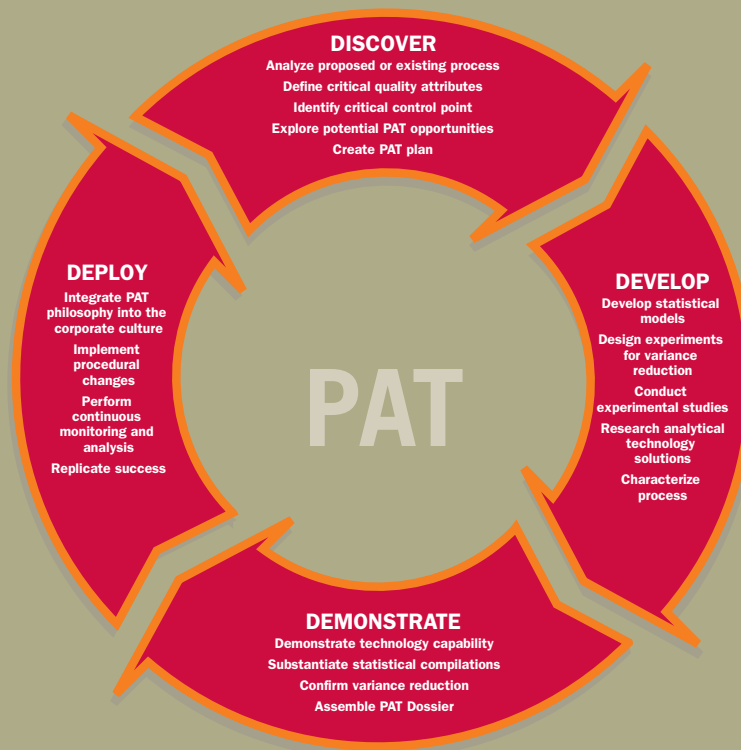


Figure 4.

# IMPLEMENTATION METHODOLOGY

## STEP 2 – DEVELOP

The development stage involves creating detailed process understanding as well as understanding through analysis, experimental studies and research of solutions. Task areas include:

- : Develop statistical models.
- : Conduct experimental studies.
- : Research analytical technology solutions.

At the end of this stage, there should be a series of solid, statistical and experimental models. These should have associated PAT solutions which enable the creation of a consistency in the process validated by successive experiments and supported by statistical models.

## STEP 3 – DEMONSTRATE

This is the point to tie in all three components of the PAT application: the analytical instrumentation, the data management, and the statistical reporting, and demonstrate its capabilities as an integrated system. There are no guidelines at present for the number of batches necessary to demonstrate the success of the consolidated PAT system. Sufficient data must be collected to show that the technology is functioning reliably and to establish a baseline for the in-process and critical quality attribute performance by analyzing intra- and inter-batch variability. There are a number of possible approaches suggested for performing demonstration batches. The approaches differ based on how processing set points and ranges are handled.

The final point in demonstration, prior to deployment of the system is to compile a PAT dossier which will gather all the learning assembled by the team and ensure that the FDA has solid documentary evidence of the rigour with which a PAT strategy has been defined and enabled in the organization. The PAT dossier should be the key source of information and be used as a live document to collect new learning. Since the post-PAT environment will involve a continuous analysis and learning process, the dossier will be a basis for the training of staff and a communication tool to inform and justify the new strategy to the FDA.

## STEP 4 – DEPLOY

PAT must be, as stated earlier, a core philosophy rather than a measurement technology or a 'flavour of the month'. It requires a new way of thinking, aggressive goals for continuous improvement with attendant measures and executive level commitment. The establishment of a successful PAT project team who have completed the first three stages resulting in an operational PAT-enabled environment should be a catalyst for change. The team should be used to 'seed' the new philosophy, including the concepts, tools and necessary changes to the entire organization. From the Automsoft experience, the initial successful project has yielded such consistency and quality that the challenge has been to prioritize from amongst the enthusiastic constituencies in the organization who want the same benefits immediately.

The establishment of this as a catalyst for profitable change will require solid organization-wide training. It will also involve the implementation of procedural changes and continuing monitoring and analysis in order to sustain and improve on the initial benefits, although subsequent improvement is likely to be less dramatic than the initial impact.

When GE wished to initiate Six Sigma across the organization, there was initial resistance. Investigation of attitudes showed that it was seen as positive but not career enhancing to be placed in charge of quality management. The introduction of a prerequisite period of time spent in quality management in order to achieve career progression turned attitudes on their head and ensured that overnight, quality became central to the organization. In the same way, PAT is a new way of thinking with enormous bottom-line impact. Whatever approaches are taken to encourage adoption, its true success will come when it takes on a key role at the center of the organization.

# CONCLUSION\_

PAT is here to stay. The drivers of PAT are not just the FDA, but bottom-line profitability on the part of the industry. Implementing PAT can be done on a modular basis, which will minimize disruption but it must be implemented on a planned, methodological basis. Data management is the component which will form the bedrock of any PAT strategy. Effectively planned and implemented data management as part of a PAT strategy will eliminate any islands of data, enable continuous monitoring and also enable continuous improvement of the process.

Automsoft has a long history of delivering value in the life sciences industry. Automsoft is committed to providing integrated, scalable solutions that specifically address the data management issues that PAT programs present.

For more information, go to [www.automsoft.com](http://www.automsoft.com), e-mail us at [info@automsoft.com](mailto:info@automsoft.com), call us on +353.1.449.1100.

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