



**PAT: EXPLORING THE NEW  
PHILOSOPHY OF THE FDA**

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In keeping with our philosophy, this Automsoft White Paper explores in a non-aligned way, the emergence of Process Analytical Technology, the FDA position on this development, implementation guidelines and a practical interpretation. Automsoft White Papers are developed as a stimulus for considering the implications of new challenges to industries and practical responses to these challenges. We share this knowledge on a broad basis to stimulate discussion, to confirm our position as thought leaders on issues of strategic importance to the life sciences sector and to assist in the development of our industry.

# INTRODUCTION\_

We believe that PAT represents the most significant shift in regulatory thinking, and consequently in the manufacture of pharmaceuticals (and subsequently biologics) in decades. We see it as innovative, exciting and, above all, challenging for the industry. This document is intended to explore this emerging area and the implications of the FDA's new positioning and philosophy in a practical sense.

There is a growing mood of enthusiasm in the pharmaceutical manufacturing industry for the many potential gains offered by the adoption of Process Analytical Technology (PAT), heightened by the September 2003 publication by the US Food and Drug Administration (FDA) of its draft document "Guidance for Industry: PAT – a framework for Innovative Pharmaceutical Manufacturing and Quality Assurance." It aims to describe a regulatory framework that will encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance. The FDA assumption is that the industry will be working with existing US regulations, but in that context has developed an innovative approach to help the pharmaceutical industry address many of the technical and regulatory issues and questions that will arise.

## PAT WHAT IS IT? \_

The 'Guidance for Industry' document makes it clear from the outset that the FDA is determined to encourage manufacturing innovation and to reassure manufacturers that they will not lose out by moving towards PAT-based manufacturing. It emphasizes, however that it sees FDA personnel working in close cooperation with the individual manufacturers as a key component in the process of implementing PAT: "The framework we have developed has two components:

- (1) a set of scientific principles and tools supporting innovation, and
- (2) a strategy for regulatory implementation that will accommodate innovation.

Among other things, the regulatory implementation strategy includes creation of a PAT Team approach to CMC review and cGMP inspections and joint training and certification of PAT review and inspection staff. Together with the recommendations in this guidance, our new strategy is intended to alleviate the fear among manufacturers that introducing new manufacturing technologies will result in regulatory impasse. The Agency is encouraging manufacturers to use the PAT framework described here to develop and implement new pharmaceutical manufacturing and quality assurance technologies."

The expected outcome is that the industry will be encouraged by the FDA to adopt innovative technologies to increase quality without concern that a new approach will lead to validation risks and production delays.

On the process aspect, the emphasis is on process understanding. In this context, process understanding refers to ensuring that sources of variability are identified and explained, variability is managed by the process and product quality can be predicted.

Historically, the approach to regulating quality in the manufacture of pharmaceutical products has resulted in high levels of rejected product, quality of manufacture issues leading to product recalls and very limited adoption of new technologies in the manufacturing process.

Following validation, the process of 'freezing' production systems acts as a clear disincentive to the adoption of new technologies. The alternative to this 'freezing' in the past has been to incur what for many is an unacceptable risk of regulatory uncertainty. The result of this historic approach has been that the manufacturing techniques of pharmaceutical manufacturing lag far behind those of industries most would consider much more primitive.

## WHY PAT? \_

In its draft guidance, the FDA has made it clear as in preceding public statements that it believes that PAT should help manufacturers develop and implement new efficient tools for use during pharmaceutical development, manufacturing and quality assurance while maintaining or improving the current level of product quality assurance. The latter point is of course the key one from the FDA point of view, since its prime objective and raison d'être is the enforcement of quality standards for the US public.

The use of the term paradigm shift is always dangerous, leading as it does to accusations of meaningless descriptions popularized by consulting firms. However, the emergence of PAT and the publication of the guidance paper by the FDA represent a shift in attitude and thinking of the FDA that is clearly dramatic. Instead of pursuing the existing system and philosophy of 'inspected quality', a move to a system of continuous quality management supported by key enabling technologies will act as a spur to a new era in pharmaceutical manufacture.

# PAT A PARADIGM SHIFT\_

"The discussion around PAT and what we might call the underlying philosophy has now been around for some years – so much so, in fact, that it is just evolving into something larger as an industry term. We are all searching for a new and higher level of 'quality by design' in manufacturing processes for which PAT is now a useful shorthand," says Dave Rudd, Pharmaceutical Development Manager with GlaxoSmithKline in the UK. He served on the FDA PAT sub-committee as an overseas member for two years, so he is both an expert on current PAT thinking and someone with useful insights into the US-based FDA decision making process and the complex meshing of different interests and approaches that it represents.

"The drivers for PAT are coming from the regulatory side, where the FDA has become very conscious that its traditional approvals procedures were actually tending to inhibit innovation in manufacturing – and causing frustration amongst the manufacturers. Its own professional resources are also stretched thinly at all times, so PAT offers possibilities for more efficient fulfillment of its mission by streamlining cumbersome procedures and focusing on the professional expertise it actually needs in the organization." He also believes that the PAT initiative is essentially just one element – the toolbox, as it were – of a grander scheme, a higher-level quality system based on Good Manufacturing Practice philosophy. The FDA is also moving towards re-evaluating what is meant by 'compliance' and quality assessment of operations. This is why it has brought in the two components – science-based and risk-based – to ensure that compliance assessment and product approvals are done on a more informed basis than the primarily empirical measurements of the past. Rather than placing a blanket policy across all of the tiniest elements it is looking to a more balanced approach, placing greater emphasis on the areas of greater risk, e.g. where a process is subject to variation and where that variation could possibly contribute to patient risk. It is also showing awareness of sophisticated new risk assessment tools that can help the FDA itself do its job better.

In the meantime the current economic climate means that there is a very clear business driver as the industry is also looking for more efficient and therefore lower cost production methods along lines that have been proven in other major industries. "There is a culture in pharmaceutical manufacturing to benchmark against each other – and manufacturing processes and procedures are very traditional in many respects, like batch manufacturing with product testing at the end of the cycle. There are long cycle times and we tolerate a relatively high level of waste. But if we benchmark profitability against other industries, say on the simple basis of total manufacturing costs against total revenues, pharma is on a par with food but way behind beverages."

"The possibility of enhancing profitability with no penalty – and even significant gains – in terms of quality assurance is an attractive possibility for the board level decision makers in the industry. Top management support is certainly critical across the sector, because of the major commitment of resources and professional time required. On the other hand, the only metric on the quality side is the absence of problems in the future. Boards have to look at returns when considering investment and PAT shows promise of contributing to enhanced profitability but there is as yet no proof of quantifiable returns."

# DEVELOPMENT AND IMPLEMENTATION OF A PAT PROGRAM\_

As PAT evolves in practice it seems clear that the role of IT will become increasingly important. The FDA itself points to four categories of IT tools for:

- : Multivariate data acquisition and analysis
- : Modern process analyzers or process analytical chemistry
- : Process and endpoint monitoring and control tools, and
- : Continuous improvement and knowledge management

That suggests a requirement for the acquisition and recording of vast amounts of data, with storage and retrieval for subsequent analysis or as the basis for modeling exercises. In this context, Dave Rudd's view is that PAT is a development function and "You develop your process understanding in the development, so that is how you decide

what monitoring and control you might later require on a routine basis. I think that at first you simply throw everything you can think of at the 'problem' but as you learn you later reduce it to as simple a level as possible in routine applications. If your development process is sufficiently robust, that should be sufficient."

"One thing we have done in the PAT philosophy is to take the focus away from the end product and place it very firmly on the process. We are aiming to develop and control processes in such a way that the quality of the product is guaranteed. Now the way we define quality is in relation to the specification for the finished product. But maybe we shouldn't! Maybe we should develop a specification for the signature of the process so that instead you now say 'When

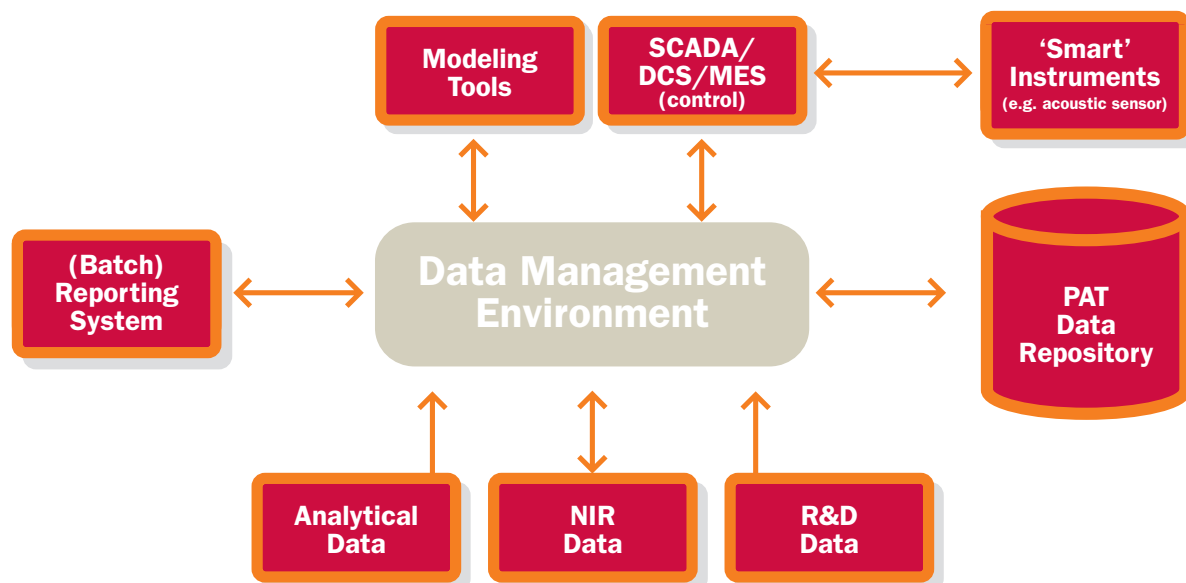


Figure 1.

# DEVELOPMENT AND IMPLEMENTATION OF A PAT PROGRAM

the signature for the process is re-created, then the quality of the product is guaranteed.' That can still apply when you transfer or scale up or change equipment."

Implementation of a PAT program will involve the identification of the relevant technologies which can be applied, creation of a data management environment capable of handling the volume and types of data to be recorded and a series of visualization and analysis tools to manage the continuing identification and prediction of stages in the process. Surrounding the infrastructure is a defined process which describes the individual elements, the continuous management model and the controls and monitoring elements including the human aspect.

**Figure 1** is a schematic representation of a (typical) PAT framework. Data and metadata from the PAT systems (and R&D data) may be filtered to discard any unwanted data (signal noise) and are stored in the PAT repository. This data is made available to the reporting system for reporting and analysis. The modeling tools provide the modeling functionality and these models may be extracted and inserted into the repository.

The critical component is, as described earlier, the data management environment which acts as an integration point, providing visibility at a sufficiently granular level of the various kinds of data and measurement activities taking place in the system.

Dave Rudd's belief is that IT systems can bring together a wide range of diverse information sets – spectral data, temperatures, flow rates, acoustic data – to get the big picture, the process signature. "But I don't think there is much out there yet that can do that for us. Yes, we can bring together all of the MSPC [Multivariable Statistical Process Control] stuff but there is also more fragmented, qualitative judgment type information that it must handle."

Automsoft's technology, RAPID-Pharma, is one of the few database software environments in the world, which can collect, store and retrieve millions of data points per second (to microsecond intervals), compared to thousands for other products. Coupled with the capability to manage terabytes of data online, this breakthrough technology is poised to become the PAT data management environment, PAT repository and batch reporting system.

Clearly any new (or recent) paradigm shift, such as the adoption of PAT, will meet with a set of both real and perceived barriers. Barriers to the wholesale adoption of PAT may be categorized as follows:

- : Historical
- : Cultural
- : Organizational
- : Regulatory
- : Technical

# BARRIERS TO IMPLEMENTING PAT

## HISTORICAL, CULTURAL AND ORGANIZATION BARRIERS

We can consider the first three items on the list together. Any profitable enterprise may well have difficulty in adopting the new work practices, technology, and techniques mandated by PAT manufacturing environment. It's often the case, in such organizations, that the philosophy 'if it isn't broke, then don't fix it' is applied. This philosophy may well hold true for some manufacturing processes where the batch yield is sufficiently high and considerable capital expenditure is invested in plant, control systems and validation for example. In this case adoption of PAT from an organizational perspective may not make sense. This is not resistance to change by an organization, instead it is a pragmatic approach when evaluating where and when to use PAT.

Resistance to change however may be an issue when examining the culture of an organization. Changes in work practices will be required in the 'ideal' PAT adoption model, where the possibility of real-time release may be realized. This would diminish the need for off-line laboratory analysis of product and could have severe repercussions with laboratory staff. The good news is that although the need for off-line analysis may be reduced in a PAT environment, it's our belief that there is still a place for it even in such an ideal environment, as the laboratory testing should act as final verification that the PAT process has executed as designed.

It's our strong belief that the broadest opportunities for employing PAT (in an end to end process) is in the NDA area. Partial PAT adoption is appropriate for processes which can clearly benefit from new instrumentation to correct (or mitigate against) a problem in the production process. For example, a plant may choose to deploy an (ultrasound) acoustic sensor coupled to a granulator to ensure consistency of the granulated particles, in the face of raw material variability, but will leave the rest of the process and equipment as before. An approach, such as this does not necessary lead to the PAT goal of complete process understanding, but will aid adopters in delivering better quality product at lower cost.

## REGULATORY BARRIERS

Regulatory concerns are often cited as a valid reason for not embracing PAT. These concerns typically relate to a lack of FDA guidance and understanding in this area. While it's true that there have been delays in regulatory approval the recent draft guidance document from the FDA on PAT represents a significant advance in this area. The guidance document is a draft and is subject to review or even withdrawal (though we believe this is highly unlikely), and does not cover biotechnology products. We expect that biotechnology products will be addressed in the final guidance document, and are happy to see that the FDA did not delay the release of the guidance document to cover this area. The guidance document is a practical guide for those organizations intending to implement PAT, and covers the areas of process understanding as well as outlining where PAT fits with the FDA's 'Risk Based Approach'. Automsoft believe that the final version of the guidance document, when it becomes available, will put to rest any remaining regulatory concerns, from the 60-day review period.

There are valid concerns however that data from a PAT environment may be interpreted incorrectly by the regulators (or even internal staff). This requires that regulators accept an organizations PAT methodology and are capable of development, implementation and validation of such a methodology. The formation of the FDA's PAT Team and the publication of the draft guidance document are a big step toward realizing those goals.

# BARRIERS TO IMPLEMENTING PAT

## TECHNICAL BARRIERS

The technology to realize a PAT environment is now effectively mainstream, thus we believe that there are no real technical barriers to deploying a PAT based production process. Tools and techniques such as Near-Infrared (NIR) spectroscopy has been used successfully in other industries since the 1960s. The same is true of (passive) ultrasound technology and stereo (machine) imaging which have been used successfully in the semiconductor industry for many years.

As described above, although the hardware technology used by a PAT implementation is commonplace, the software infrastructure to manage a PAT process is nascent. For example, it remains to be seen what the canonical form of a (complete) batch record would look like and whether there is any commonality across different PAT processes and organizations. (Note that the FDA does offer some suggestions in the draft guidance document, but there is clearly some way to go before a common batch record format can be developed.)

A perceived technical barrier is the lack of software infrastructure to manage the data from a PAT process. This barrier has been breached 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. The system has been designed to cope with very large volumes of data, such as high frequency spectrograms from NIR devices, and can also warehouse 'traditional' process data such as that from SCADA and DCS.

Dave Rudd points out that for once the FDA and the pharmaceutical industry are approaching a set of issues with no particular conflict of interest, although there are certainly very different perspectives. The FDA is now very committed to the application of PAT, he believes, both for ab initio process development in new product manufacturing and also for retrofitting where applicable to elements of the approved manufacturing processes for the current product portfolios of the major manufacturers. It is offering the comfort of a 'safe harbour' approach to any difficulties that may occur (provided always that no question of patient jeopardy arises) as a result of the application of PAT in consultation with the FDA team. This is one area where the industry is probably still a little wary, he believes, because of course there are as yet no precedents. The FDA has become something of a technical enthusiast in promoting PAT but conservatives in product manufacturing and internal regulatory groups have a valid objection in that there has to be some element of running a higher risk of product approval being denied or delayed.

# HOW PAT WILL SHAPE MANUFACTURING OPERATIONS IN THE FUTURE

In GlaxoSmithKline, the policy is that PAT has to be project driven and developed alongside promising new chemicals that are working through the company's product development system. Even in backing likely winners the approach will be to proceed with a dual approach – traditional and PAT-based manufacturing processes – so that solid comparative data can be obtained. Pursuing this course for a year or perhaps two, Dave Rudd explains, would enable accurate comparisons from all points of view and, assuming success, would serve to validate the qualitative results of the PAT-based systems against the currently orthodox systems that have regulatory approval. In an industry that has long lead times and economic cycles, is there any danger that PAT is an interesting line of fashionable thought that will duly disappear as something newer comes along? "I certainly don't think that PAT is an initiative that is going to be superseded. I have got to know the FDA processes and the key players and am convinced that the encouragement to the industry is from the heart," says Dave Rudd. "The Guidance document is a very clear indicator of the Agency's official line of thinking and there is also, I believe, a clear expectation that the industry will in fact follow along. There is certainly nothing of the mandatory at this stage but in the time frames when we can expect PAT to be well embedded in the manufacturing side of our industry – say two to four years – who is to say that it may not be the only route to approval for the manufacture of new products?"

In Automsoft, we also believe that the technology described as data acquisition and analysis will yield benefits not only in optimization of production but also in overcoming the hurdle that scale-up currently represents for the industry. The ability to track and analyze movements in variables at a granular level, and the application of similar technologies in laboratory and production will deliver a substantial shift in visibility.

Process Analytical Technology and the FDA support for a PAT framework is a significant breakthrough for the manufacturing aspect of the industry. We believe it will usher in a new era in manufacturing of pharmaceutical products and enable the industry to capitalize on innovative technologies to increase quality and reduce costs, in the same way as less regulated industries.

# CONCLUSION\_

In terms of a regulatory approach to PAT, the draft document describes a highly collaborative approach to a regulatory framework to support the use of innovative technologies. It is proposed that PAT tools and technologies will be proposed to the Agency during the development phase, although there is encouragement for the use of PAT strategies for currently manufactured products. The use of terms such as 'flexible' and 'facilitate' indicate an active approach on the part of the agency to support and encourage the adoption of process analytical technology. The regulatory strategy includes a PAT team approach for cGMP inspections, although this is not clarified in the document. It is proposed to undertake joint training and certification of PAT review, inspection and compliance staff and scientific and technical support for these staff.

From all of this, we conclude that PAT is here to stay, it will become mandated in elements and it will be eventually applied to the manufacture of biologics. We also conclude that this is a breakthrough for both the industry and the FDA and, given the current availability of the relevant technologies, including Automsoft's RAPID-Pharma, is capable of immediate implementation. Indeed, we are aware of at least five of the major pharmaceutical companies who have PAT programs currently under way. We are entering a new era in pharmaceutical manufacture and we in Automsoft are excited to be a part of it.

## BIOGRAPHIES

### **DAVE RUDD: GLAXOSMITHKLINE**

Dave has worked for GlaxoSmithKline Research and Development in the Pharmaceutical Development group for over 20 years. During this time he has been involved in most aspects of new product development, but has placed greater emphasis in recent years on the interface between R&D and manufacturing. A long-time champion of the use of Process Analytical Technology to improve product development and manufacturing efficiency, Dave was an active member of the FDA Process Analytical Technology sub-committee which helped to formulate the recently-published 'Guidance for Industry - a framework for innovative pharmaceutical manufacturing and quality assurance'.

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Paraic O'Toole is Chief Executive Officer of Automsoft. Prior to joining Automsoft in 2001, he was Vice President-Western Europe of Cambridge Technology Partners responsible for building European divisions of the business. He is a serial entrepreneur, having founded a number of companies in the software and consulting fields. Paraic holds various qualifications in marketing and computer science and is a frequent speaker and author on topics concerned with leadership, management and innovation in the 21st century economy.

### **IAN PEPPER: AUTOMSOFT**

Ian Pepper is Chief Technology Officer of Automsoft. Prior to joining Automsoft in 1999, Ian held senior technology positions in US and Irish companies and has worked on products ranging from state of the art artificial intelligence tools, to financial modeling, to automated distributed test tools. Since joining Automsoft, Ian has spearheaded the design, development and management of the RAPID product suite. He is a frequent speaker at industry conferences, and has authored a chapter in the book "OPC - OLE for Process Control". Ian is a joint holder of multiple software patents used throughout the RAPID product suite. He is a member of the ISPE.

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