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Perspective

The need for a broader perspective if process analytical technology implementation is to be successful in the pharmaceutical sector

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Process analytical technology (PAT) has the potential to deliver significant shifts in the economics of the pharmaceutical sector. In the two years since the FDA published its guidance on PAT in 2004, there has been a wealth of research and comment articles on its adoption by the industry. This article discusses whether the literature matches the reality of the challenges faced inside companies, whether company practice and studies take too narrow a view of PAT, and what issues should be considered if the full potential of PAT is to be achieved.

Three striking themes – backward process analytical technology (PAT), narrow PAT and inward PAT – spring out from our review of recent literature and also our experience of how pharmaceutical companies are implementing PAT [1]. First, there is a tendency to work backward, getting priorities reversed by an undue focus on the analytical technology at the expense of the business outcomes and the process frameworks. Second, PAT is often viewed too narrowly, with a focus on the technology alone without proper consideration of the wider context in which it has to be implemented. Third, much of the discussion around pharmaceutical PAT is inward with little learning from outside the industry, despite the fact that the pharmaceutical sector is relatively late in its introduction of PAT. A wealth of accumulated knowledge exists in industries like food and petrochemicals. Some of this reluctance to learn from other industries might come from an uncertainty of how to adopt PAT from non-FDA-regulated industries to a highly FDA-regulated industry.

Backward process analytical technology

Our 'backward' theme comes from the observation that some companies and commentators almost seem to be working their way backward through PAT. Instead of maintaining focus on what PAT has arrived to do – namely to provide a framework for process understanding and control (the P in PAT) – there is a greater emphasis sometimes placed on the analytical technology and the analysis (the T and the A). For example, a common approach is to focus on rapid analytical technology for the replacement of traditional laboratory testing. Perhaps this is not surprising in the light of one survey of 18 pharmaceutical manufacturers, including 12 in the USA and six in Europe, which found that the understanding of PAT varied considerably: 'participants [in the study] diverged in their perceptions of how broadly PAT is defined. Some see PAT as primarily an initiative to provide quality data during the manufacturing process through on-line, rather than laboratory, analysis – a

Continued on page 20.

Journal of Pharmaceutical Innovation

somewhat limited view of PAT. Others understand PAT in a broader context of scientific principles: process understanding, risk-based approach, integrated systems approach, and real-time release (RTR).' [2]. The limited view of PAT is often reflected in literature that hails the benefits of a particular piece of technology without any emphasis on or referral to the 'broader' goals that are at the heart of the PAT initiative [3].

There is a tendency for companies to think of PAT in terms of current validation and quality-control processes. The current focus is on the sensor and what it can measure rather than the wider quest for process understanding that should be determining the choice of technology and the design of the system. Thus, some companies become caught-up in the effort of replacing current measurement systems with a technology that provides analytical results more rapidly. No wonder Ajaz S. Hussain, who at the time was deputy director of the Office of Pharmaceutical Science, Center for Drug Evaluation and Research, at the FDA, reminded companies: 'you've got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product' [4].

While the current literature does emphasize the key concept of improved process understanding, it rarely goes beyond this context either to make a connection downward to the practical issues of implementation faced by a company wishing to pursue PAT, or upward to the wider business benefits that can flow from PAT. We believe there would be significant utility from greater exploration of the reasons for this divergence between theory and practice. In our experience, many companies are introducing analyzers to replace laboratory methods, but struggling to close the loop, that is, to use the analytical results and link them to feed-back or feed-forward control actions. Part of the problem, as we have seen, is that these companies are starting with the perspective that PAT involves replacing current laboratory-based systems with online sensors rather than taking a more holistic PAT design viewpoint.

Narrow process analytical technology

There are many other reasons that PAT is not implemented as it was intended. A key factor is the tendency for PAT to be the responsibility of a relatively narrow team of people. Implementation projects often lack a multi-disciplinary approach with the result that companies run the danger of simply reinforcing existing approaches rather than more open-mindedly questioning the current quality principles and methods and exploiting the full potential of PAT. This is reinforced by the pressures of some company cultures. As one author wryly observed, there is an inclination by some companies to say: 'We bought you the hardware, now do something' [5]. In such a climate, and reinforced by targets and reward systems, there is often pressure to develop PAT with a narrow perspective and to avoid the creation of multidisciplinary teams that might add to the impact of the initiative. This is a significant problem because effective PAT implementation needs to cross traditional boundaries.

In many respects, the research literature also neglects looking properly outward from the process-understanding context to the wider business and patient benefits that this goal must serve. The immense scope for savings in the pharmaceutical manufacturing industry from a philosophy based on the principles of PAT is generally well understood. After all, the FDA makes the point vividly: 'A recent estimate [6] of potential worldwide cost-savings from efficiency improvement is suggested to be as high as US $90 billon. This would be equivalent to the current cost of developing 80 to 90 new drugs every year.' [7]. Although by other recent estimates, the equivalent number of new drug applications would be as low as 45 to 50 [8]. However, despite this compelling evidence, the territory between the macro-overview and the technological detail has not attracted adequate study. Indeed, the FDA goes on to note that 'a rigorous economic analysis to obtain robust estimates of cost savings may help to put an end to the lingering question – 'how could this be possible?' – and to fully engage the pharmaceutical community for developing approaches to realize the potential 'win-win' opportunities' [8].

One of the issues that pharmaceutical manufacturing plant managers continue to struggle with is making the business case for investment. For example, a quality assurance director participant in one study remarked: 'I do not think that everybody understands clearly what PAT is, and what the benefits could be for the industry... It is taking time to identify an area, a single area, where we could apply some of those technologies and see results' [2]. The experience of AstraZeneca in Sweden is instructive. In an article reporting on the challenges of implementing PAT over a 10 year period, Ulrika Henningsson writes: 'The key is to integrate PAT tools in the supply chain management from R&D to commercial manufacturing and use them to improve quality consistency, shorten cycle times, and minimize losses. Thereby, benefits can be quantified in an appealing way to get the necessary support from senior management.' [9]. The same author goes on to emphasize just how important the internal business case is. Despite the regulatory and other outside momentum behind PAT, she concludes 'the greatest challenge though, has been to convince the organization and train the people to understand the point of PAC/PAT. The technology in itself has shown to be the tip of the iceberg – people are the foundation!' [9].

Part of the business case challenge again reflects our 'narrow' theme. Often the case is framed from the narrow perspective of particular job roles. Scientific personnel, when asked to make an estimation of the business gains, will often restrict their calculation to a comparison of the current laboratory method with the cost of a replacement analyzer without looking at the much bigger gains to be achieved by fully closing the loop to achieve real time release of product and continuous manufacturing. Even the production personnel, who should

have the greatest focus on productivity, will fail to look wider than their own plant. As one commentator observed:

> '...most discussions to date relate only to performance of a single product. One should also consider deploying an enterprise-wide approach to PAT... Consider, for example, a high-volume product manufactured at more than one facility. A direct comparison of multiple manufacturing trains within and between facilities becomes possible. The performance of raw materials can also be assessed across multiple product lines in which they are used and additional understanding obtained relative to their performance for the company. Similar assessments could be made of manufacturing equipment across multiple product lines.' [10].

Another way in which we believe discussion of PAT is framed too narrowly is the scope of potential PAT benefits. For an existing production process, PAT adoption and implementation tends to be seen in terms of reduced cost, lower inventory levels, and a move toward just-in-time production and supply. For new processes, the benefit of PAT is the ability to quickly develop the manufacturing process, upscale to a robust process, and perform validation more easily. These are tremendously important, but the full business case and competitive advantage potential also needs to be seen in the context of the end consumer or patient. The 'process understanding' that lies at the heart of PAT means that manufacturers can gain improved process knowledge and production capability to create products more rapidly to match the quality and therapeutic expectations of patients. PAT not only enables manufacturers to gain improved control of their product quality, but also enhances a company's ability to match different patient needs better. This is significant because bioavailability differences are, of course, important for drugs with a relatively narrow therapeutic index and also because of the potential of PAT to deliver a competitive advantage by shortening new product development.

Inward process analytical technology

Several signs of the industry's inward view of PAT exist. It is rare to see 'competitive advantage' being mentioned in the literature. Considering the fact that patient safety is a primary motivating factor for PAT, it is surprising that the link between PAT and individualized drug therapy does not receive more attention. Again, we would contend that this is a result of the tendency to look inward at the technology rather than outward at either the business or the patient perspectives. Perhaps the most significant example of inward thinking is the general failing of the industry to take advantage of the available PAT lessons from industries where the technology is now well established.

It is our strong belief that the pharmaceutical industry should take advantage of the significant PAT experience accumulated by other industries. Our industry must overcome its cultural antipathy to such comparisons. Academic study can help by filling the gap in cross-industry learning and knowledge (for example, see Ref. [11]). The attitude that the industry is somehow unique from other industries is too prevalent. The unfortunate consequence of this attitude is that little concerted effort has been put into studying the experiences of industries such as petrochemical, chemical, electronics, aviation, aeronautics, and others. But perhaps the challenge lies in how to adopt the PAT experiences from these non-FDA-regulated industries to an industry that is regulated by the FDA. A notable exception is the active participation of the pharmaceutical sector on the cross-industry work carried out by the US Center for Process Analytical Chemistry [12]. However, most of the thrust of this work is on the challenge of technology transfer from the academic to the commercial arena rather than the issue of technology transfer between industries.

Conclusion

Greater focus on the PAT experiences from other industries will enhance the efficiency of PAT development in the pharmaceutical sector. While successful PAT implementation depends on new technology, appropriately broad organizational and business perspectives are critical for success. Current corporate practice and academic study should avoid a narrow focus on analyzer technology. The industry will not realize the full potential of PAT until the process understanding–process control that is the foundation of PAT provides enhanced product quality, reduced time-to-market, and the facilitation of improved patient safety and competitive advantage.

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