MANAGING RISK AND DRIVING PROFITABILITY WITH TODAY’S PROCESS ANALYTICAL TECHNOLOGIES IN THE PHARMACEUTICAL INDUSTRY
Executive Summary

Over the past few decades, terms such as Lean Six Sigma, Total Quality Management, and Continuous Improvement Strategy have become increasingly common in discussions of manufacturing plans. These techniques have one goal in common: to develop processes that maximize productivity and consistency and minimize risk to workers, consumers, and to the company. But each of those methods addresses specific aspects of manufacturing quality and efficiency. At an advisory board meeting with the FDA in 2011, one pharmaceutical industry executive concluded, "The industry started by controlling variability using Six Sigma, and then moved onto reducing waste with Lean Manufacturing. It’s possible to do both without QbD (Quality-by-Design). However, without QbD, one can apply Lean and Six Sigma to everything rather than focusing on issues that are critical to product quality.”

The essential value a QbD approach brings to process design is in identifying what process parameters most affect product quality and then devising control strategies to assure consistent quality production.

Early adopters of such evidence-based statistical strategies for process control and improvement include aerospace, automotive, and electronics industries, among many others. These industries have strived for efficiencies far exceeding 6σ, as the risk of not doing so far outweighs the cost of implementation of these process control strategies.

The pharmaceutical industry continues to play catch-up with other industries in the adoption of these process development and improvement strategies. That fact is supported by numerous reports of process inefficiencies and product recalls. In a benchmark study by G.K. Raju of MIT, he claimed, "It was taking an average of 60 to 90 days to manufacture and release a batch of tablets that should be made in one 8-hour shift. Much of that time was spent on deviations that needed to be investigated and on testing.” And even as recent as 2014, several large pharma companies reported plant utilization at around 50%.

There are a variety of reasons that pharmaceutical companies have been slow to adopt change. With the average estimated cost of bringing a drug to market starting at $800 million, the pharmaceutical business is built on a delicate balance between tight developmental timelines to provide clinical trial materials and optimizing process development for understanding, control, and cost reduction. Since these processes are fixed in place by Phase III clinical production, this conundrum to date has greatly prohibited the incorporation of new process or analytical technologies.

Outmoded technologies and methods are often deployed in a large number of these plants. And the process parameters affecting product quality are not always understood. Due to inefficiency and waste, it can cost 2–3 times more to make a drug than it costs to research and develop a drug and bring it to market. And the need to notify regulatory agencies of any deviations from the filed process can result in potentially costly requalification and subsequent regulatory approval, further discouraging process improvements.

The motivation to develop and bring products to market as quickly as possible is driven by market economics. From the moment a company submits an application for IP, the clock of profitability begins to tick. Industry experts estimate that it costs a drug company $1 million for each day a product is in development and more than $0.5 million in unrealized revenue for each day a product commercialization is postponed.

As products come off patent, there is incentive for innovator companies to protect profitability by locking out generics for as long as possible. One effective strategy is to incorporate as much drug substance and drug product knowledge as possible into the NDA filing, making it necessary for the generics to demonstrate comparability for all that is present in the filing. This point becomes particularly important in light of the reality that while the number of new drugs being brought to market decreases, the cost of bringing them to market continues to rise. Also of financial concern to pharmaceutical companies are the pressures of reducing healthcare costs, especially within the United States. Companies are finding it increasingly necessary to investigate strategies for decreasing costs for drug development and commercialization while assuring that those products provide maximum profitability and quality.

The drive to find and adopt new technologies for process development and control is clear and has many motivations, all of which directly relate to productivity, profitability, and risk. It is estimated that as much as 10% of medicines produced annually don’t meet specification and must be discarded or reworked. With an average pharmaceutical process efficiency of less than three sigma, it is not surprising to see the high rate of drug recalls over the last decade. This can damage a company's reputation as much as its bottom line. Between reject and recall batches, the pharmaceutical industry loses approximately $50 billion per year.

At the same time, the global demand for pharmaceutical drugs continues to increase, as is exemplified by the growing rates of diabetes worldwide.
Long HPLC runtimes are no longer a hindrance to the decision-making process. Here, a 25-minute HPLC analysis was run in 2.5 minutes using UltraPerformance LC® (UPLC®) with no loss of resolution between analytes.

The need for regulators to assure public safety and an uninterrupted supply chain has led them to encourage pharmaceutical companies to develop processes with greater understanding and control, as is standard in many other industries. This effort resulted in the release over the last decade of a set of guidelines promoting quality and process analytical technology (PAT) initiatives. 9,10 These initiatives focus on risk-based and QbD principles, where processes are well-characterized through identification of critical quality attributes and the process parameters that have a large effect on them. Through a series of design of experiments (DoE) that measure the impact that changing process parameters have on critical quality attributes as well as any interaction effects from the multiple parameters, greater product and process understanding is gained.

This richer design space knowledge provides manufacturers with the opportunity to confidently and flexibly optimize processes for throughput and yield. It is important to note that gaining process understanding is an ongoing task that begins in the development of a process but continues well after product release, and is an essential part of the continuous improvement strategy that is also promoted within the regulatory guidelines. While the transfer of that understanding to manufacturing is assumed, it is often overlooked that the migration of knowledge from manufacturing back to development is equally critical, not just for that product but other similar processes in the production facilities. Therefore, the selection of analytics for process monitoring can have a large impact on future development efforts, when data can be easily correlated throughout the product lifecycle.

Though the business case evidence for QbD is slow to come, there are companies talking publicly about the realized benefits of QbD practices in NDA filings. With unexpected increased demand for a particular product, an executive at one such company reported that the process flexibility afforded by the QbD filing allowed them to optimize the process parameters within demonstrated design space to meet the demand.1 He went on to further say that with the continuous improvement strategy of QbD, process capability improved from 3-4σ at launch to 5-6σ within six months. This example demonstrates that while there is cost associated with adopting QbD in development, the payback for that investment is largely post licensure in manufacturing.

While acceptance of the benefits of QbD is growing, adoption of these approaches and technologies has been slow. There are several perceived challenges with a QbD and PAT approach, including initial investment in infrastructure and qualified personnel for implementation, additional time to establish new development workflows, and regulatory uncertainty with this approach and approval for QbD filings. The regulatory bodies do recognize that while they aren’t able to mandate QbD filings at this point, they do need to be more proactive in guiding and encouraging companies as to what those dossiers must contain in order to speed up and assure approval.5 Though QbD and PAT are not yet requirements, current regulatory process validation guidance has incorporated parts of ICH Q8, requiring a shift towards QbD to achieve compliance.5 Also, to promote and
accelerate the adoption of PAT technologies by pharmaceutical companies, the FDA is streamlining the regulatory process for new technology adoption and harmonizing regulatory expectations. As companies explore technologies to provide them with a richer understanding and control of their processes as defined in the regulatory guidelines, there are a few requirements that those tools must meet to be successful in helping companies achieve their productivity, profitability, and risk goals. Any PAT tool deployed in a process development or production setting must, above all else, be rugged, to minimize the risk of downtime. It must also give accurate measurement results reliably that truly reflect the state of the process and product quality, time and time again, from one system and facility to another. And, for the sake of ensuring that the skill set of the individuals on the manufacturing floor is focused on the process rather than the analytics, the PAT tool should be easy to use. Automation helps to reduce human-induced variability that can confound process understanding and control. For companies to overcome the resistance to adopt new technologies and strategies there must be a high degree of confidence that there will be a predictable and significant return on that investment.

As pharmaceutical companies have developed new products and processes, state-of-the-art technologies have been investigated and selected to replace less reliable and less sensitive ones. From 2000 to 2006, spectroscopic techniques found the largest growth (48%) for use in monitoring chemical manufacturing processes. Liquid chromatography (LC) and mass spectrometry (MS) experienced less growth during that same timeframe. Given that these are techniques that are used heavily during the characterization phase of discovery and development as well as for release testing of final product, the slower adoption of LC and MS technologies (28% and 15% of total process analytics market respectively) is not due to insufficient information gleaned from their use. In fact, many companies value the information they provide enough to employ them offline for the verification of product quality and process control. Often, this results in either delay in forward processing while awaiting analytical results or uncertainty about product quality when analyses performed after process step is complete.

If companies value the information they get from liquid chromatographic techniques enough to resort to offline analyses, it is only natural to wonder why those techniques aren’t embedded in the process. While the benefits of LC for identifying and quantifying both abundant and low level components in a complex mixture are well documented, laboratory-based LC makes it less useful than other techniques for process monitoring. There are several reasons for this. For LC analysis to be performed on a sample, it must be withdrawn from the process. In addition to interrupting the manufacturing process and reducing the yield, sampling is thought to increase the risk to the sterility or integrity of the batch. High performance LC (HPLC) analyses have also historically been too slow for real-time process decision making – it can take hours for results to arrive from the laboratory. And, whether or not it is deserved, there has long been a perception that HPLC is less reliable and requires a high degree of specialization in the skill set of the workers using it, leading many companies to rely on offline analytical lab analyses where need exists for the information provided by HPLC. Because time equals money, process downtime is a large hurdle to overcome.

Spectroscopic sensor technology such as Raman, NIR, and FTIR does not disrupt the process and requires little direct intervention by process personnel. While these benefits are readily apparent, some sensors are sensitive to moisture and therefore require additional drying steps in order to get quantitative information about the process. These sensitivities can result in additional unnecessary process steps that have the potential to contribute greater variability to the product. Sometimes, even with processes designed around the sensors’ requirement for analysis, not enough information about the samples’ Critical Quality Attributes (CQAs) are obtained, such as distinguishing between similar species or quantifying process and product impurities in addition to target product. In such cases, offline analysis of process samples is employed (often times LC analyses). These offline analyses either idle the process while awaiting results, or forward processing continues without real-time evidence of a process in control. It also limits the ability to control the process in real-time.
A New “Gold Standard” In-Process PAT Tool

Nearly a decade ago, LC technology took a major leap forward with the introduction of newly-designed instrumentation and separations chemistries. Waters® introduced ACQUITY UltraPerformance LC® (UPLC). Erasing the old notions of HPLC, the new breed of instrumentation brought dramatic improvements in speed, resolution, and sensitivity. With these gains in performance came a greater depth of sample knowledge with every analysis in a fraction of the time it previously took.

It became evident to drug companies that the improvements in productivity and the attendant speed of decision-making brought to the laboratory by these new technologies would also likely benefit the process development and manufacturing functions. Discussions between pharmaceutical companies and Waters Corporation led to the subsequent introduction of a process analysis technology that is profoundly affecting how drugs are manufactured. No longer is it necessary for process development chemists and engineers to send out samples for analysis and wait hours for the results. Instead, with online or offline sample acquisition, results of quantitative analyses are available and can be responded to in near real-time, making it a valuable tool for both process scouting experiments as well as process control feedback/feed-forward strategies.

The PATROL UPLC® Process Analysis System is capable of generating multipoint calibration curves from a single standard vial and manage sample-specific dilutions in a programmable workflow to give near real-time quantitative results, even as concentrations of product in the process change. The result: improved throughput, reduced material waste, optimal resource utilization, and reduced process and measurement variability. Today’s process analysis systems can communicate to a plant’s distributed control system (DCS) or LIMS for full integration into a process workflow for monitoring and control.

Adoption of online UPLC has the potential to have an immediate impact on the bottom line for a business. In one instance, a process development lab learned it could cut the time it takes to manufacture a batch of one drug by 75% if they let their process analytics tell them when maximum yield occurred. With online UPLC process analytics as their guide, another manufacturer found they could save over $1 million annually for one product by reducing the amount of catalyst required during the process.

PATROL UPLC Process Analysis Systems are readily configurable and scalable from the lab environment of early process development through process optimization and intensification and into process monitoring and control on the production floor. The application of the same high quality metric throughout the development can translate to faster time to market with a depth of process understanding previously capable only through offline measurements. The information provided by PATROL UPLC Process Analysis Systems to the DCS can be used for real-time feed-forward and feedback action to be taken, providing greater ability for process control.

For facilities requiring chain of custody documentation for samples, the barcode reading capabilities and CFR 21 Part 11 compliance of PATROL UPLC Process Analysis Systems meet regulatory requirements in an electronic format that further eases burden in the workflow. Evidence of traceability is automatically captured in the Empower® Chromatographic Data System (CDS) and readily accessible for audit.
It is important to consider when generating a large amount of complex process data that without the ability to easily search and extract meaning from that data, little can be done in terms of process improvement. PATROL UPLC Process Analysis Systems running on Empower Chromatography Data System come equipped with NuGenesis® Software Data Management System (SDMS) to aid in managing and accessing the information collected. The application from Paradigm™ Scientific Search Software can further enhance users’ leverage of the available information by enabling specific chemical and biological information searches across multiple enterprises within a plant.

Improvements in separations technologies, like UPLC, are enabling manufacturers to reliably obtain the mission-critical go/no-go information they have required. Today’s technologies are ideally suited for QbD efforts, as encouraged by regulators. Deployment of these robust UPLC tools in process development and production promises improved process efficiency and understanding along with minimal measurement related variability. Additionally, data from process development, scale-up, and production can be readily correlated to that of upstream and downstream processes for further process understanding and enhancements.

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View Application Notes and Product Info

References

9. USFDA Current Good Manufacturing Practices (cGMPs) for the 21st Century.
10. USFDA Guidance for Industry PAT.