Using Lean to Catalyze Pharmaceutical Product Development

R&D must harness its inherent scientific horsepower and apply it through statistically unbiased experimental designs.

BY BIKASH CHATTERJEE, PRESIDENT AND CTO, PHARMATECH ASSOCIATES

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As a scientifically based industry, we have relied on data to drive our decision-making. There has been a great deal of focus on adopting tools to reduce cost and increase overall business performance. Yet only recently, in the last five years, have we begun to look deeper and consider the concepts behind operational excellence as opportunities to catalyze overall business development. Few can argue the value of the application of Lean principles, Six Sigma, Kepner-Tregoe and TRIZ on a project-by-project basis. However, their impact in terms of transforming our business competitiveness is still debatable. Part of the reason people are not shouting the benefits of these tools from the highest mountaintop is that we are early in our journey to competitiveness. We are starting from a position where our organizations reward us for arriving at our final destination, not for the path we took to get there.

Transforming a business framework means changing thinking as well as tools. The latest FDA and ICH guidance documents attempt to do this by demanding a higher level of scientific understanding at the process development level as a new foundation for quality assurance. These are radical departures from common practice and represent an enormous hurdle to future regulatory compliance. Adding to this complexity is the immediate need to improve business performance. While this is nothing new to business, I believe the paradigm has changed somewhat. Historically, within the pharmaceutical market, the formula for profitability has always been:

Standard Cost + Profit = Market Pricing

This formula reflects a marketplace that will pay for whatever the industry provides and could represent what we call the “good old days” of the seventies and eighties. Today we find ourselves faced with a slightly different perspective to business competitiveness and a formula for profitability that looks more like:

Market Price - Standard Cost = Profit

This is a subtle but significant shift that recognizes the reality of market pricing caps and focuses upon managing overall standard cost to realize profit. Renewed interest in the Operational Excellence tools mentioned above is largely related to this shift in thinking. The question facing us is how much more can we extract from our shop floor processes and remain competitive? Most supply chain strategies involve a component of overseas manufacturing to return immediate cost savings. However, as these markets struggle to develop a stable quality mindset, they also represent heightened quality risk. Some organizations find the risk too great and have limited these sites to supplying product to markets where the compliance and regulatory requirements are not as high. While this may not be as lucrative in the short term, such a strategy may bring a significant long-term revenue stream as these markets mature.

To better manage compliance risk, Big Pharma is setting its sights further upstream in the development lifecycle, looking at early pre-clinical activities as an opportunity for cost savings. Both clinical trial activity and investments by pharmaceutical companies to expand presence in Asia are accelerating. A recent market analysis ranked China as the top destination in Asia for Big Pharma [1]. The report suggests that

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Asia outsourcing is moving up the value chain, as low-cost production is eclipsed by a broad range of factors, including market potential and R&D capacity as the drivers of growth.

Pharma has always recognized the importance of strong R&D in terms of overall corporate health. Despite a weak economy over the past nine years, America's pharmaceutical research companies have consistently invested around 18 percent of domestic sales on R&D activities [2]. The question before us now is, can we do better, reduce the cost of product development and perhaps reduce the time to market for new products? The application of Lean and Six Sigma in the development environment is a hallmark of the best-in-class companies that compete in rapidly changing markets to produce consumer goods, but it is largely unknown in the pharmaceutical industry.

Lean Product Development

Toyota's approach to product development has been considered the benchmark in terms of both efficiency and effectiveness. While recent events have cast some doubt on Toyota's ability to execute against their plan, I feel they do not diminish the value of the underlying strategy. A recent 30-month study conducted by the University of Michigan identified seven fundamental principles that account for Toyota's speed-to-market [3]:

1. A holistic, systems approach to product development
2. An embedded customer-first approach to product development
3. A front-loaded process
4. Built-in learning and continuous improvement
5. Synchronize processes for simultaneous execution
6. Use rigorous standardization to create strategic flexibility
7. Go-to-the-source engineering

While these principles were developed for heavy industry, the underlying philosophy speaks directly to the product development challenges faced by the pharmaceutical and biotech industries as well.

A Holistic, Systems Approach to Product Development

This may seem obvious at first but surprisingly few R&D organizations are structured around the concept of efficiency and effectiveness. Typical organizational structures are divided by therapeutic area (e.g., cardiovascular, oncology), and their support functions, (e.g., toxicology, pre-formulation). This results in isolated sub-groups that make accountability and monitoring very difficult. Many large R&D organizations resemble a multi-armed octopus, making a common vision impossible to communicate and embrace.

An Embedded Customer-first Approach to Product Development

This is a complex concept for most development organizations. With the recent events in the U.S. healthcare market and looming pressures from the universal healthcare policy recently approved by Congress, it has never been more important. The voice of the customer (VOC) concept is the foundation of operational excellence principles such as Six Sigma and Lean manufacturing when analyzing value-added business practices. The development concept of VOC must be translated into terms which are relevant within the development culture. These would include key product performance characteristics that define the form, fit and function of the product, but should be expanded to include downstream considerations such as scalability, formulation sensitivity to variation and identification of critical process variables. While not strictly VOC, these metrics can be considered Critical to Quality Attributes (CQA) that

result in achieving the VOC goals.

A Front-loaded Process

This point includes the notion that decisions made during the development phase dictate the flexibilities downstream in commercial production. Establishing a clear framework for measuring R&D effectiveness stems directly from this concept. To be effective, R&D must broaden its approach to discovery, harness its inherent scientific horsepower and apply it through statistically unbiased experimental designs that employ appropriately powered sample sizes. Studies must extend to understanding the sources of variability within the formulation and how the process can affect overall product performance. Practitioners of this approach attest to the enhanced product development timeline predictability that is derived from this approach, and also to the cost savings downstream due to the ability to make changes quickly, at small scale.

Built-in Learning and Continuous Improvement

These concepts denote a fundamental shift in most R&D environments that are based upon specified knowledge and understanding. Built-in learning, or Knowledge Management (KM), is the cornerstone to uniting a disparate organization. KM focuses on ensuring critical discovery and because learning is disseminated throughout the organization, it can improve the organization as whole, not just on isolated projects. Too often product design and development are left to the experience of an individual or departments responsible for the program. When this occurs, the result is redundant development of products that could have been considered as platform products, each going through their own process of discovery and learning. And this translates to additional complexity through the supply chain and manufacturing process, all which become sources for variation with the organization and add to the overall standard cost.

Synchronize Processes for Simultaneous Execution

Building upon KM provides an opportunity for orchestrating processes. One approach that may work well within the pharmaceutical development environment is the concept of Set Based Concurrent Engineering (SBCE). SBCE allows multiple development decisions to remain open until they must be finalized.

In pharma, where safety, dose ranging and clinical efficacy are not often well understood until the very end of the development cycle, this approach allows milestone development activities such as specification development, technology transfer and key process parameter identification to begin in parallel as the product moves through the development lifecycle. Eliminating an excipient that cannot be sourced reliably or standardizing key processing steps can dramatically stabilize a process downstream if the evaluation is initiated early when minor changes can be addressed.

Use Rigorous Standardization to Create Strategic Flexibility

As the hallmark of Operational Excellence principles, this concept is initially counterintuitive. Standardization allows an organization to focus on the technical challenges of product development rather than the procedures or metrics around the organizational process. Rigorous standardization facilitates process predictability and allows better planning and decision making throughout the development process. Establishing pre-defined milestones and success criteria makes the development process measurable, discourages improvised decision making and allows R&D to prioritize more effectively.

Go-to-the-Source Engineering

This concept simply points out that it is easier to develop a robust and effective product if you understand how it will be manufactured and what can go wrong. The more exposure development scientists have to the practical variables that affect manufacturing, the more easily these issues can be addressed in the product design phase. For example, watching manufacturing during a screening operation and observing screen blinding may prompt a developer to implement a particle size specification that describes the desired particle size distribution. Understanding the end of the process allows the developer to compensate during the design process.

Conclusion

The R&D environment constitutes a significant opportunity for improving business performance. The success metrics defined by ICH Q8, 9 and 10 represent a significant challenge for our industry and will ultimately require us to change how we develop new products within the development pipeline. Applying

Lean principles to the development process can provide the upstream impetus to catalyze tremendous downstream efficiencies that will translate to improved business performance and overall competitiveness.

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