Why quality-by-design should be on the executive team's agenda

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Better practices in product and process development could raise the profits of pharmaceutical companies by up to 20%. Now is the time to implement Quality by Design.

New product development in the pharmaceutical industry is costly and time-consuming, and it often results in products that are expensive and difficult to make. It's getting harder to find safe and effective new products, but much of the expense, delay and rework in drug development occurs outside the clinical development process. Product and process development (PPD)[1]—the activities that include active ingredient manufacturing, formulation and analytical method development, regulatory review and approval, validation and preparation for commercial manufacture—account for 15 to 30% of overall R&D expenditures. Even more important, PPD directly determines production costs before and after commercial launch.

Of course, pharmaco executives are generally aware that their non-clinical development processes are less than ideal, but many

1 Product and process development (PPD) refers to a set of processes in pharma also known as chemical and pharmaceutical development (CMC), pharm sci, process development and tech development.

don't make a concerted effort to improve PPD. They may be focused on the demands of clinical trials, which largely determine whether a product gains approval for commercial marketing. Some don't believe better PPD can deliver the benefits in pharma that it has in other industries. Others think they have implemented the right tools and processes, but few companies use those tools systematically enough to reap their full benefit.

New approaches to manufacturing have clear benefits for patient safety and quality, but in this article, we focus on PPD improvements, which offer significant opportunity for value creation. Our models suggest that ineffective PPD is costing companies up to 20% of their potential net profits. Organizations across the industry that embrace the challenge can significantly reduce costs, improve products, shorten time to launch, reduce risk, and improve patient benefits. We estimate that for the industry as a whole, this opportunity could represent an incremental $20 billion to $30 billion in profits.

Building effectiveness in

Product development in nearly every industry is a major, complex undertaking, and pharma is no exception: development takes an average of four to eight years and about $1 billion (Exhibit 1). In most industries, most of the final cost of a product is determined early in the development cycle, when product parameters are defined. Thus, product development processes have a high impact on eventual manufacturing efficiency.

exhibit 1

Industry	Time Years	R&D capacity MY	Budget $ millions
Civil aircraft	4-7	5,000-10,000	2,500-5,000
Automobile	2.5-5	1,000-2,000	500-2,000
Pharmaceutical	**4-8**	**500-1,000**	**500-1,500**
Stationary gas turbines	3-5	500-1,000	300-500
Railroad rolling stock	2-3	50-400	20-160
Consumer electronics	0.5-1	10-100	5-50
Consumer durables	0.5-1	2-20	1-10

SOURCE: McKinsey

In pharma, PPD represents about 15 to 30% of overall R&D cost and time, can influence up to 50% of total R&D cost, and is a key determinant for all costs of goods sold from active pharmaceutical ingredient to final packaged product. And PPD is a critical contributor to the quality of the final product.

The efficiency of commercial pharma manufacturing operations established during product development lags other industries, despite similar expenditures. For instance, overall equipment effectiveness (OEE)—a standard operational performance measure—is 35-40% in pharma[2]. In consumer packaged goods, an industry with comparable processes, OEE ranges from 70 to 90%. Even comparably regulated industries, such as aerospace, regularly achieve average OEE rates above 50%. Pharma has a compelling case for increasing development cycle performance to reduce cost and bring the industry in line with others.

The QbD potential

To tap the PPD improvement potential, companies must adopt a new paradigm commonly known as Quality by Design (QbD).

One reason QbD has so much impact is that it enables companies to quickly amass and apply knowledge that is critical to the commercialization strategy. The more efficiently companies build this knowledge—including technical requirements, product profile, and regulatory compliance needs—the better they can use it to develop commercial manufacturing processes that minimize cost and risk, and maximize profits over a product's lifetime. Companies can accumulate this knowledge through more intelligent PPD investment and standardization of product development and technology platforms.

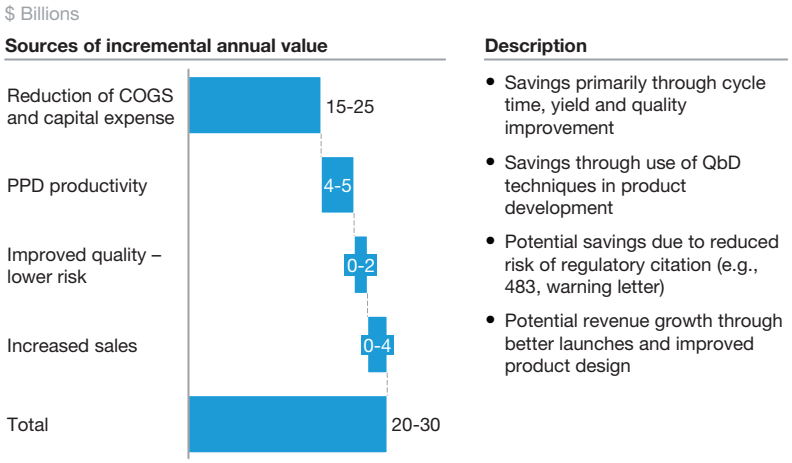
In addition to higher quality end-products, PPD offers many benefits: lower costs, shorter time to launch, improved patient benefits, and increased sales. We used a bottom-up approach to size the potential for pharmacos by quantifying each of these sources of value and estimating the impact of implementing QbD on an individual compound, a company, and the innovator pharma industry as a whole. We quantified the value PPD improvement brings, using conservative assumptions backed by industry experience and concrete examples.

We believe that improving PPD can increase an individual compound's lifetime value by 30 to 50%. Across a portfolio of compounds, this translates to a

2 McKinsey's proprietary operations benchmarking (POBOS) measures OEE at plant and line level for multiple technologies

reduction of 10 to 20% in annual COGS and 20 to 30% in PPD spending. Theoretically, across the entire innovator pharma industry, it represents an incremental $20 billion to $30 billion in annual profits (Exhibit 2).

exhibit 2



Note: Pharmaceutical industry COGS estimated $145-166 B, PPD spend estimated $15-17 B
SOURCE: McKinsey

We estimate that optimizing PPD practices would reduce COGS by 10 to 20%, which could produce $15 billion to $25 billion of annual savings on the industry's $145 billion to $166 billion COGS. In calculating this value, we included a reduction in manufacturing defects, cycle time, compliance cost, and commercialization cost, together with an increase in yield. For example, savings derived from cycle time reduction alone result in a 5% reduction in COGS.

Most important, companies can realize savings through QbD techniques without increasing PPD costs. Implementing QbD on the $15 billion to $17 billion industry PPD baseline can reduce PPD costs by $4 billion to $5 billion. In addition to value gained through operational efficiency, companies can find value in reducing compliance remediation costs and improving product-development-enabled sales, such as novel dosage forms or line extensions. We think some quality issues attributed to PPD could be avoided, which have imposed $1 billion to $2 billion in direct remediation costs on the industry from 1997 to 2006. The associated indirect costs—lost sales, manufacturing

inefficiency, consulting fees, etc.—are easily in the billions of dollars. Improving PPD would prevent some of this waste.

Finally, PPD can increase revenue by ensuring smooth scale-up and product launch, and make it easier for companies to create differentiated products. The industry now derives at least $3 billion to $4 billion of value by through PPD-enabled sales. We estimate that PPD can further increase sales by up to $4 billion.

A large pharmaco, for example, failed to meet sales forecasts and overshot target COGS for an in-market pediatric product. Marketing and manufacturing executives were interested in reformulating the product, modifying the pricing structure, and making contracting changes. They engaged the PPD group within the company for assistance. Marketing surveys showed that patients would pay more for a pediatric liquid formulation than a solid formulation. The company implemented a QbD program to execute the new formulation. As a direct result of the program, the company developed the liquid formulation on time and within budget, and sales for the drug increased 48%.

Taking down the barriers

So what are the obstacles to widespread PPD improvement in pharma? The biggest one is the practice of transferring clinical trial production methods to commercial manufacturing. The driving force in PPD is speeding development in the clinical trial phase and producing drugs quickly so that the next clinical trial can launch without delay. Unfortunately, processes that are appropriate in trials may not be efficient for mass production. These sub-optimal processes often become the production processes for the commercially manufactured drug because management does plan for the optimization of these processes as part of the ongoing development and life-cycle management process.

The result is a variety of underdeveloped and inefficient product development practices: sub-optimal concepts, a lack of understanding of physiochemical process interactions, missed product parameter targets, high failure rates, long timelines, and inadequate prioritization. These problems are apparent in the high variance across the pharma industry of key aspects of product development, including the degree of development at different phases, investment strategy and governance models. This unevenness points to opportunities to identify and implement best practices.

A second obstacle to PPD improvement is an industry-wide tendency to point toward regulation and the governing bodies that enforce them as a primary source of development and manufacturing woes. Other regulated industries such as the aerospace and nuclear industries have very stringent rules, but continue to manufacture a much higher percentage of defect-free products.

The widespread use of QbD techniques in these industries enables them to achieve efficiency and extremely high quality despite regulatory restrictions which are similarly, if not more, stringent.

Seven years have passed since the FDA began to push the pharmaceutical industry to revolutionize how it develops and manufactures products and processes. Five years have passed since the adoption of regulations (ICH Q8 and Q9, Q10) meant to facilitate the implementation of QbD. But little has changed in most pharmacos. Today, as investors and the public push for increased ROI and quality from pharmacos, companies and regulators have an exceptional opportunity to join forces to push for better processes and lower costs through improved PPD.

Some industry proponents argue that pharmacos cannot adapt the QbD tools and technology from other industries to PPD without significant investment. Fundamentally, we believe that the tools are available and applicable in pharma and that skeptics underestimate QbD's potential.

Implementing QBD

Implementing QbD is complex and challenging; many of the concepts, frameworks, and tools are new to pharma PPD practitioners. As in any operational transformation, adopting QbD requires a cohesive set of technical tools, management infrastructure (such steering mechanisms and key performance indicators), and new mindsets and capabilities, including a training infrastructure, a knowledge base, and a high-performance operating culture within the PPD group.

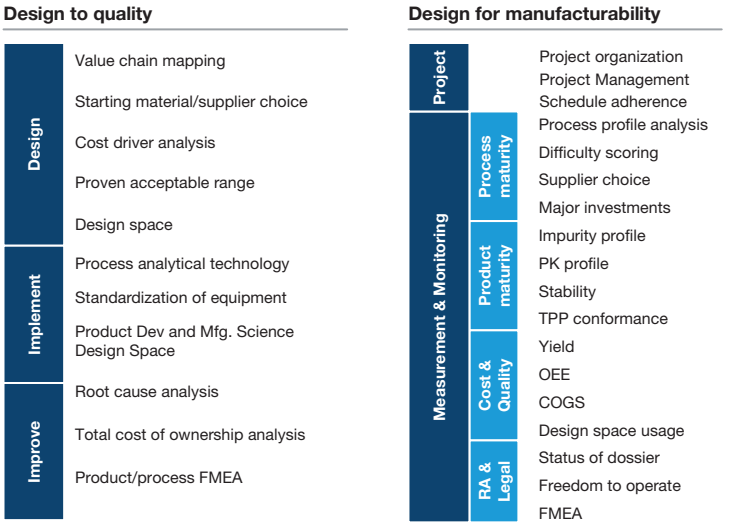
But unlike lean programs, which pay off fairly quickly, the benefits of QbD may take three to five years to appear because it takes so long for pharma products to reach the market.

Many concepts have been associated with QbD, as evident in numerous publications and conference presentations. Generally, implementing QbD in pharma involves the combined application of design space, process analytical technology, statistical design of experiments, technology standardization, designing both production and quality methods according to the principles of "Poka Yoke" and even the introduction of new technology.

In our opinion, QbD also should include time-tested methods based on best practices in other industries and tailored to pharmaceutical development, like value stream mapping, design-to-cost and process risk analysis. The implementation of these tools does not require new regulations or guidance, as a handful of pharmacos have demonstrated, just dedication and know-how.

In practice, a QbD program is an integrated set of innovative techniques for designing high-quality products based on the most critical customer needs and compliance requirements at low cost (design to quality), along with methods for optimizing these new product designs for commercial manufacture (design for manufacturability. This combination creates a regimented yet smooth development process that yields superior quality, cost efficiency, and risk reduction (Exhibit 3).

exhibit 3



SOURCE: McKinsey

To govern the application of the new process, the PPD team should pass through a series of quality gates where predetermined product parameters must be achieved.[3] Managers control investment in drug candidates as they mature and move through the development process, and apply tools to ensure quality in the manufacturing process.

One international pharmaco, for instance, suffered from high costs in newly developed products and a lack of governance in the quality department in PPD. Individual products were up to 100% more costly than company executives estimated would be financially healthy. To reduce costs and improve quality, the company introduced a QbD program. Executives trained

3 For more on quality gates see "Quality gates: Raising the standard of pharmaceutical technical development" on page 204

employees in QbD tools and implemented a standardized project governance process that checks the application of those tools.

This approach guaranteed that PPD focused not just on R&D timelines, as before, but also on overall production process quality and cost. Executives understand that the application of QbD tools is not just mechanical, so they invested in creating a culture focused on the whole approach—for example, by introducing a shared language to communicate quality standards, exchanging people and knowledge across projects, and, perhaps most important, ensuring that QbD appeared on the top management's agenda.

CEO support

Implementing QbD requires investments in change management to ensure that the new methods stick. This requires a strong commitment from the executive team, including the CEO and his or her team, an overarching governance structure, and rigorous project management.

As a vital component of profitability, PPD requires that cross-functional performance objectives are in alignment. To ensure this, the CEO must create a compelling business case that lays out the company's overall objectives and each department's role in achieving them. Efficient PPD often entails multiple departments working in concert, including manufacturing, quality, regulatory, and R&D. Making the right tradeoffs between short- and long-term objectives, and among sometimes conflicting departmental needs, requires clear direction and strong arbitration.

Next, the CEO should build a strong and committed top team to provide direction and support to individual departments. Together they should craft a story to communicate the upcoming changes that excites people but limits the changes to those the company can realistically bear. It is important that all employees are clear on the high-level objectives and understand how they can contribute.

The top management team has an essential role to play in cascading the CEO leadership and direction to the senior management of the individual departments, so the changes may be integrated appropriately with other organizational processes. Improving PPD through QbD is primarily about execution, not approving higher levels of R&D investment. Delegating the task exclusively to the front line will not work. Naturally, scientists, engineers, experts, and smart regulatory negotiators are essential to a QbD program. Senior management must be educated enough to ask their scientific staff the right questions: not just "Is the project on time?" but also "What are the key risks?" and "Have we considered alternative designs?"

Implementing QbD takes a long time and requires active executive management throughout the process. To be successful, the program needs the support, governance, and cultural experience of the top team, who must be willing to make QbD a priority and act as role models through their own behavior. The top team should be visibly involved in a selected number of initiatives to send the message that solid progress is expected and will be rewarded.

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We believe that the pharmacos, regulators, and the public at large can gain much from the broad-based adoption of QbD in the pharma industry. Not only are the benefits great: the opportunities are apparent. Perceived barriers to implementation are just that; supposed but not actual barriers. Companies that have successfully implemented QbD have shown that the rewards are worth the effort. We believe that pharma CEOs, COOs, R&D heads, heads of PPD and regulators alike should seize this opportunity.