

Product Development: Challenges and Recommendations

Abstract

Developing a therapeutic biotechnology product is both capital and time intensive. In part, the two factors go hand-in-hand: the science behind new therapeutic takes time to develop, which equates to increasing capital expenditures. The question for biotechnology firms is whether they can do something to reduce their costs and the time it takes to develop a new product. In this paper, we discuss how the system surrounding drug development – regulatory process, public demands, and competitive environment – affect the cost and time associated with product development. Then, based on interviews with biotech management, we suggest steps that firms can take to manage the development process.

Introduction

The often cited cost of drug development - \$800 million, after accounting for the cost of capital over the lengthy development cycle that extends from 12 to 15 years - has come to represent an accepted, if obvious fact: developing a new prescription drug is costly^{1,2}. This paper draws on the insights of biotech managers and current literature to present key drivers and recommendations for minimizing the cost and time associated with new product development*.

One of the key factors that account for the high cost and lengthy time associated with drug development is the *science*. The business of biotechnology is an endeavor that is not only science-based, but also relies on real-time advances in science to produce new products. The cost and time needed to develop a new product is driven, in part, by the largely unknown science behind new therapeutic products. Unlike many other industries, breakthroughs in biotechnology, although significant, tend to be only a small part of a very large picture. New research and tests provide new data that might explain why a previous rationale didn't work or might point to a new mechanism of action that wasn't known before. However, individual studies rarely expose the whole picture – the size of which is unknown. Part of the difficulty with biotech products is that they are intended to solve *unmet* medical needs. Were the science well developed, thoroughly understood, and easily applied, the need would be met. However, the fact that many diseases have no known cure indicates that despite decades of scientific research and remarkable advances, we still lack understanding of the science behind many disease and treatments. For this reason, a product candidate might pass Phase I and Phase II studies but fail when placed in the Phase III placebo-controlled study. Alternatively, sometimes the process is lucky; the candidate works even when all the reasons are not well understood.

* This paper is based on a case study that involved extensive interviews with seven members of the top management team for a small clinical-stage biotech firm. The views and insights shared by these individuals are augmented with examples and findings presented in both periodical and scholarly work

In addition to the uncertainty of science, other factors also affect the cost and time of drug development, which are not tied to the science at all. Instead, these factors relate to the system that guides drug development. This system includes:

- An extensive *regulatory process*, with its overarching objectives and step-by-step study phases,
- *public demands* that have influenced the regulatory requirements that biotechnology companies must meet, and
- The *competitive environment* that requires strong intellectual property (IP), large sums of capital and a host of organizational choices related to strategies and structures that help advance the product development process.

New drugs are regulated by the Food and Drug Administration (FDA) in a process (depicted in Appendix A) which takes 12-15 years and limits a firm's ability to reduce product development time. Issues at the FDA, including changes in leadership³, the perceived effect of ties to industry of those leaders⁴, reduced funding^{5,6} and the loss of skilled individuals who understand the latest in science^{7,8} have affected the time it takes to get a drug from initial discovery to market approval. Programs meant to help expedite development of new drugs[†], while helpful have not always achieved expected results. The mission of the FDA may also create some inherent tensions; the FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human drugs and biological products *and* helping to speed innovations that make medicines and foods more effective, safer, and more affordable⁹. While commendable, the goals of safety and speed often work in opposition of one another. A complete safety profile for a new product is developed only after many years of extensive, and costly, testing.

Public sentiment can also affect the cost and time it takes to produce a new drug. News of adverse events related to drugs, like the related risks and deaths associated with Vioxx and adolescent anti-depressants have led to public outcry, increasing the pressure on the FDA to increase safety¹⁰. Public demands to limit these 'avoidable' deaths has led some to question whether the FDA has been sufficiently aggressive in monitoring drug safety and these critics point to serious deficiencies in how the FDA regulates prescription drugs¹¹.

Financial regulation also contributes to the cost of drug development. Fueled by public outrage over several major corporate accounting scandals (e.g. Enron and WorldCom)^{12,13}. The Sarbanes-Oxley Act of 2002[‡] has also affected the cost of drug development. Costs associated with SOX 404[§] compliance have proven to be significant. According to the Financial Executives International (FEI), in a survey of 217 companies with average revenue above \$5 billion, the cost of compliance was an average of \$4.36 million¹⁴. However, for small biotech companies it is not uncommon to spend \$500,000 or more per year. These compliance costs

[†] Two such programs are *Subpart E* in Section 312 of the Code of Federal Regulations which establishes procedures to expedite the development, evaluation, and marketing of new therapies intended to treat people with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternatives exist (*Federal Register, October 21, 1988*) and *Accelerated development/review* which is a highly specialized mechanism for speeding the development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists (*Federal Register, April 15, 1992*).

[‡] A United States federal law Pub. L. No. 107-204, 116 Stat. 745, also known as the Public Company Accounting Reform and Investor Protection Act of 2002 and commonly called SOX or Sarbox; July 30, 2002)

[§] Under Section 404 of the Act, management is required to produce an "internal control report" as part of each annual Exchange Act report. See 15 [U.S.C. § 7262](#). The report must affirm "the responsibility of management for establishing and maintaining an adequate internal control structure and procedures for financial reporting." 15 [U.S.C. § 7262\(a\)](#). The report must also "contain an assessment, as of the end of the most recent fiscal year of the [Company](#), of the effectiveness of the internal control structure and procedures of the issuer for financial reporting."

can present an insurmountable obstacle for smaller biotech companies with limited, if any, revenue. Indeed, a small biotech can easily spend hundreds of thousands of dollars for something that is meant to ensure shareholders that they aren't at risk due to accounting practices. The Act, passed in response to these scandals may have been necessary and useful, but some believe it does more economic damage than it prevents. For biotech firms and their investors, the risk from accounting errors pales in comparison to the risk that the product fails to reach the market.

Combined, the financial and product regulatory oversight creates significant levels of regulation. With this regulation come artificially high barriers to entry, high prices, and relatively less competition than might otherwise be the case. Although product regulation is intended to ensure compliance with safety and efficacy goals, and SEC reporting is meant to reduce investor risk, both regulatory regimes increase the cost and time needed to develop a product while leading to lower levels of competition, and higher market prices of new products. Less competition and higher prices are generally not a good situation for developing new products. It's not good for companies and it's not good for consumers.

Characteristics of the competitive environment, in which drug development occurs, also affect the cost and time of product development. Key characteristics include the need for strong – usually exclusive patents, multiple sources of funding, and organizational structures that can conflict with one another. The first of these, strong patents that form the firm's IP is critical for biotech firms. IP provides the firm with the freedom to operate, while keeping others from being able to step in. Having the freedom to operate may involve in-licensing to gain rights in specific areas, while protecting from others can involve obtaining multiple patents to keep others at bay. Patents protect the right of the firm to capture value that is derived from their science-based discoveries, but obtaining this protection through patents can be more difficult than in other industrial sectors. Relative to other types of patents, the unique nature of biotechnology and its unpredictability necessitates heightened written descriptions and more complete enabling requirements (the patent must teach those skilled in the art how to make and use the invention as broadly as claimed, without undue experimentation)¹⁵. As a result, a biotech firm's IP can be very complex. Despite this, it is a fundamental requirement for small biotechnology firms.

Once patents and licenses are in place, biotech firms still need substantial amounts of capital to conduct studies and generate the data to move the product forward. Firms use several sources of capital, including SBIR grants, NIH research grants, investment from venture capital funds, and various forms of partnerships. Although many firms would prefer to go it alone, funding constraints usually mean that small biotech firms need to find product development partnerships that bring in capital and skills. However, partnerships don't always provide what is expected up front and can end prematurely, taking the funding with them.

The competitive environment surrounding development can also generate tensions between different desired and required organizational structures. For example, remaining small like a research lab can help to minimize expenses and retain agility but this limits the skills available in the firm. As the product develops the firm must grow, bringing in new people with a range of skills needed to handle the enormous regulatory requirements. There is a tension between the 'research lab' feel of young biotech companies, on the one hand, and a professionally-led group capable handling the regulatory aspects of development, on the other. As the product develops, the firm changes from a primarily science-focused endeavor to a bureaucracy with increased emphasis on managerial issues. This changes means that more people are, and need to be, involved which in turn produces more layers, requires more

communication, and results in more complicated decision networks - all of which can increase both the cost and time it takes to develop a new product.

Recommendations**

Despite the uncertainty of science, regulatory hurdles, public scrutiny, and a difficult environment, biotech firms can minimize the cost and time needed to develop new products. First, although studies suggest that it takes a very large amount of capital to develop a new product (\$800 million to \$1,200 million), not all products require such a hefty investment. This is, after all, an average. Some products will use less capital, and others will use more. Second, there are steps that firms can take to manage the development process, which may reduce the cost and time involved in developing their specific new products. Specifically:

The firm can adopt strategies and organizational design elements that help to minimize the cost and time needed to bring a product to market.

Focus the science on increasing the understanding of the product characterization and the mechanisms of action. The science behind a biotech product can be extremely difficult. However, several insights can help a biotech firm manage the scientific process. One issue to understand is that science in a biotech firm will take many forms over time. Initially, the early stages of discovery will focus on basic science. This will be augmented with testing and the accumulation of scientific data to prove the product concept. Once a proof of concept has been validated the science will be applied to the practical problem through research and development programs that are designed to support the product development effort. At each step, the science has a different emphasis that will lead to the overall objective of a new, marketable product. However, an overarching goal is to increase the product characterization and the firm's understanding regarding how the product works. With this focus it becomes apparent that moving the science along in a firm is not the same as what happens in an academic research lab. Where academic research projects nearly always produce outcomes that lead to other interesting studies that can find funding, science within a firm needs to focus on results that help move the product along. Focusing studies so they provide data that characterizes a biological can save time and money later since well characterized biological drug products are exempt from some of the more redundant tests that the FDA can require. Even with this focus, there remains the difficulty of predicting the time it will take to reach desired milestones. Generating the needed data often takes a lot longer than expected, since product development is partly a function of the significant uncertainty that surrounds the science.

Manage the regulatory process. On the financial reporting side, a firm has no choice but to manage compliance and fund the staff and reporting systems needed to meet SEC requirements. On the clinical side, regulatory hurdles can be reduced or overcome with several strategies. One tactic is to utilize thought leaders to develop the science and validate the product candidate and approach. As the clinical phases begin, it is also important to build the bureaucracy to handle the volume of reporting that is needed for clinical regulatory affairs, and put in place systems that can help the firm learn how to get through the myriad of hurdles at the FDA. Another tactic that can smooth the regulatory process is to involve the FDA, and actively seek ways to build trust. One approach to building trust is to continuously build on data, so that at each step the FDA sees the progression of development in the data presented to them. When a firm has built a good working relationship and trust, the FDA will lend considerable help and guidance, even when a product fails.

** These recommendations come from the interviews with the managers whose identities shall remain anonymous. References in this section indicate additional support for the ideas expressed by the managers.

Align capital sources with the stage of science development. In the world of scientific research, certain players (government, universities, industry) have traditionally played specific roles in scientific development. Understanding these can help a firm align its capital sources and expectations with a given stage of scientific development. Historically, government has played a large role in supporting basic science research without the requirement of an immediate application. Aligning basic research in the firm with relevant government agencies (e.g. NIH) can match expectations of timing and results with the funding source. In addition, such alignment may provide 'free' funding through grants and other government programs while tapping into pockets of expertise and provide access to additional resources (e.g. large scale clinical trials for technologies and therapies related to vaccines) that would otherwise be cost prohibitive for the small firm. As the product candidate advances, aligning with academic medical centers can allow a firm to work with the best clinicians in the area. While hurdles related to conflict of interest exist, partnerships during the translational stage of research that engage top scientists who are interested in seeing the product brought to fruition can be invaluable. In the later stages of development, industry is best suited to manage the clinical testing through the regulatory phases of development. For a small firm, partnering with larger organizations often brings in capital and provides access to develop later stage skills.

Acquire or internally develop a range of skills. Biotech firms often are founded based on a piece of yet-to-be-proven science. However, in addition to the need for skilled scientists (potentially in several different areas) the firm can help its development process by acquiring skills related to outsourcing (technology transfer, in-licensing and partnering) the regulatory process, project assessment, and financial development. For example, as the firm enters into clinical trials it needs to build a bureaucracy to accommodate clinical and regulatory affairs. With the advance of the product, the firm needs to grow, hiring skilled individuals who have experience and success with the regulatory process, clinical design and understand the value of rigorous data collection and presentation procedures.

Manage the pace of the firm's growth. While there can be a basic desire to grow, there is the need to first focus and succeed in one area before moving ahead on many fronts. To focus efforts, firms are advised to select criteria to choose among different options. These might include whether the area is interesting, there is an unmet medical need, the product can be tested in an efficient manner, it can be sold on the market at a price that rewards the firm for its effort, and it presents acceptable technical and business risks. Firms must also emphasize execution: this might mean writing product development plans that describe major issues, setting goals to achieve milestones and abandon projects if they cannot get to the goal stage. Equally important is the need to manage the pace for urgency by *slowing* things down and resisting the tendency to take short-cuts. Pacing the development of the firm can help a firm learn what works and help them manage the challenges of transitions as a product moves from one stage to the next.

Acquire an ability to change. In the course of a biotech firm's evolution, it is not uncommon for a firm to change directions and morph through several forms. There are many things that can help a firm change. At the outset, it is important to understand that things often don't work as planned and will take longer than anticipated. In addition, although there is a tendency to rush through as fast as possible, time *is* part of the process. And, if you're the first in an area, it is important to realize that you'll spend more and do more because you're the pioneer blazing a new path. For young firms working in new areas, the ability to change is also impacted by the key to minimizing the cost and time needed is to learn what works, focus on a

few things, aggressively acquire skills when needed, lead with the right skills, and train people as much as possible.

Understand your firm's chosen business strategy. The cost and time that a firm spends developing a specific product depends on the firm's chosen business strategy. While many biotech firms assume that success comes from growing and integrating new skills needed for activities that extend from research to clinical affairs to commercialization, the attainment of becoming a fully integrated biotech firm (FIBCO) is but one strategy that a firm can choose. A biotech firm might also choose to operate within the discovery and early stages of development, and follow a model of a revenue or royalty income producing company (RIPCO). With this strategy, the firm needs to concentrate on producing a very good clinical package up to the proof of concept, but after that point sells the product to another firm for further development. Compared to the strategy of becoming a FIBCO, the RIPCO firm spends less time and resources on product development.

Develop skills to raise funds through out-sourcing. Development time and progress is also critically impacted by available capital. In addition to the capital that may accompany alignment with government agencies, medical facilities, and industry partners, most firms will also require other sources of capital. Other sources of funding can include the sale or out-licensing of assets and/or various investors including Venture Capitalists and shareholders. Firms can minimize the cost of raising capital from these sources by developing outsourcing skills and by retaining investors.

Manage expectations. To retain existing investors and raise additional money as needed from these sources, the firm needs to direct expectations. To do this, the firm can manage its communication with investors, educating the investors about the next event – or the next data point and following through with timely results from real, rigid trials. If a firm can do that and the technology proves itself, investors will be clamoring to invest in the company.

In addition to the steps that firms can take to minimize the cost and time it takes to develop their own new products, there are systemic changes that would help reduce the cost and time needed to develop all biotech products. These changes are unlikely to be achieved through the efforts of a single firm. However, awareness and efforts that support these changes and are made by many firms – as well as other players - may have a significant impact on the development process.

Increase focus on mechanisms that can help realize higher levels of benefit. Recent studies have suggested that the cost and time needed to bring new biotechnology products to market are increasing¹⁶. Changing this trend will take a radical move in the current regulation and development environment. While this might seem unlikely, emerging forces may help nudge the process in the right direction. An increased focus on individualized medicine¹⁷, pressure to reduce drug prices^{18,19,20}, and an increased reliance on market mechanisms to determine usage^{21,22} can all help to reduce the cost of some, if not many, new products. Products that are designed for specific populations will be tested in smaller clinical studies – thereby taking less time and using fewer resources – while achieving higher rates of efficacy within that smaller portion of the population. While prices for these 'target market medicines' may not fall, the price/benefit ratio will change significantly making a more convincing argument for these new therapeutics. The focus of product development for sub-populations can also help to increase competition by allowing several firms to work in the same disease areas. Instead of competing head-to-head, these firms can differentiate themselves by the sub-population they target. With increased levels of differentiated competition and expanded

treatment options, patients and physicians will have many options from which to choose. Additional factors such as health insurance plans that rely on customer-choice, document product use and report therapeutic outcomes can also encourage developments in medicine since they let patients actively select plans that provide access to innovative, effective therapies.

Examine the level of safety that is optimal to obtain. A key issue that contributes to the time and cost of drug development in the regulatory process is the need to meet safety standards that are increasingly high. The FDA has as its mission to protect and ensure the safety of drugs that are available in the U.S. However, the burden of meeting absolute or nearly absolute safety standard contributes to the cost and time needed to develop a new product. These levels of safety might be too much to ask. There simply is no fool-proof way of knowing for sure that a drug is free of any safety concern. Safety – and the public’s understanding of what levels of safety can or should be achieved – has a large impact on the cost and time of product development. New approaches to thinking about safety might help to reduce the burden that current unrealistic standards place on firms and the FDA. For example, viewing a safety profile as something that develops overtime as new information becomes available might lead to the idea that the FDA can reach its safety goal and still approve new products more quickly with conditional approvals of new drugs for specific diseases and drug candidates. Conditional approvals can then be required to collect information through post-marketing surveillance (PMS) once a product is approved. Under this type of approval, the firm can use data from PMS studies and insurance data to further establish a drug’s safety profile while gaining income from market sales of the drug use for specific uses²³.

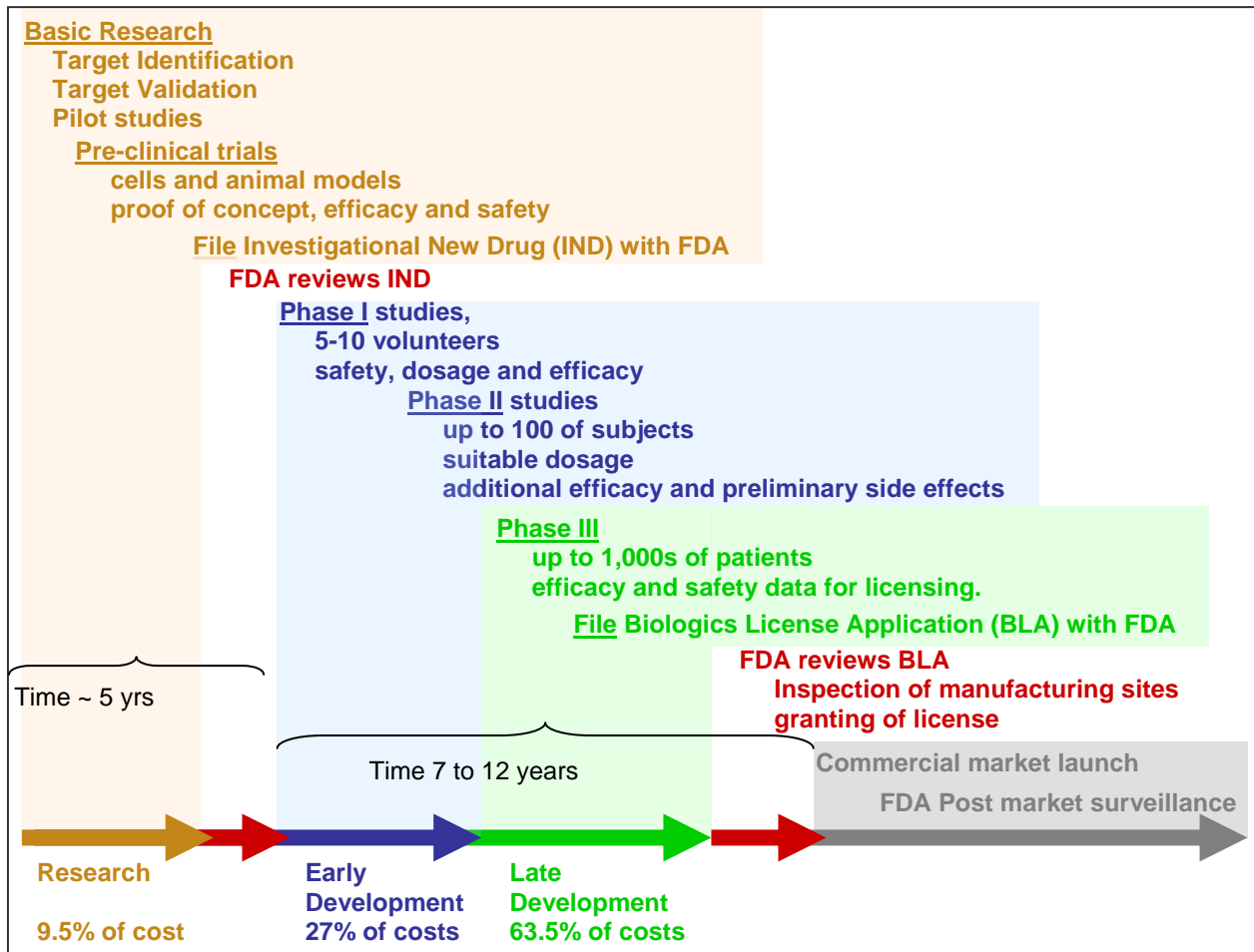
Educate the public about realistic safety goals. Additional steps to lesson the burden created by the desire to achieve extreme levels of safety without putting individuals at high levels of risk would be to educate the populous, and lawyers on the constraints that exist: nearly every drug can be toxic in at least some circumstances. Safety, as measured by the number of adverse events, can also be managed by policies that limit reimbursements for off-label use, encourage generic drugs use when efficacy levels warrant them (instead of as a general application which can lead to longer treatments due to poor efficacy) require PMS to build safety data and ultimately cover the cost of prescription drug choices when they achieve targeted levels of efficacy for specific indications.

Increase the speed at which science develops. One means of achieving this may be to look at the constraints that accompany elements of the development environment. For example, the environment requires that firms have strong patents. These patents allow a firm to operate without competition in their specific product area. While this aspect of the industry provides strong incentives for firms to take the risks involved in developing new products, and is strongly entrenched, an alternative view may be more effective at furthering the industry as a whole and developing more competitive firms. Because patents offer exclusive rights, they necessarily limit competition. However, patents – even though they provide a disclosure of information - can also limit the development of science because they limit involvement. Unlike other areas of science, there are vast amounts of knowledge which is unknown and therefore not reflected in patents. Instead, a large portion of the value underlying biological patents comes from the interpretations and the understanding that are drawn from working in the science. Since these are not shared via a patent, and patents effectively limit the number of firms involved in a given area, patents tend to reduce the cumulative development of science. In the future, policies that encourage the sharing of findings, interpretations and understanding rather than those that preserve proprietary knowledge can help to improve the advances of science^{24,25,26}.

Conclusions

Biotechnology firms face several challenges: the most significant of these relate to the time and cost that it takes to develop a new product. Part of these challenges stem from the unpredictability of the science. However, the cost and time of developing a new product is also the result of the regulatory, legal, and organizational environment in which the firm operates. Although a specific firm may not be able to radically change the time and cost needed to develop *all* new therapeutic products it can take steps to minimize the cost and time for their *own* products.

Appendix A



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