The Economics of New Drugs: Can We Afford to Make Progress in a Common Disease?

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OVERVIEW

The concept of personalized medicine is beginning to come to fruition, but the cost of drug development is untenable today. To identify new initiatives that would support a more sustainable business model, the economics of drug development are analyzed, including the cost of drug development, cost of capital, target market size, returns to innovators at the product and firm levels, and, finally, product pricing. We argue that a quick fix is not available. Instead, a rethinking of the entire pharmaceutical development process is needed from the way that clinical trials are conducted, to the role of biomarkers in segmenting markets, to the use of grant support, and conditional approval to decrease the cost of capital. In aggregate, the opportunities abound.

T
he concept of personalized medicine is beginning to come to fruition with new therapies tailored to specific populations of oncology patients. Unfortunately, these new products are being brought to market at prices of tens to hundreds of thousands of dollars per patient. Rather than just a pricing anomaly, we believe these prices reflect an unsustainable business model for this technology.1 In this article, we argue that it is essential that we re-envision the entire business model for personalized health care if we are to have a pathway forward that will sustain innovation.

The current business model supporting pharmaceutical development is based on traditional drug development in which small molecules are broadly marketed. This general framework was extended to the development of biologic products as they were introduced to the market. However, we believe it cannot be extended to personalized medicine without significant reconsideration of some of the core concepts and practices in oncology because of the increasingly prohibitive costs and the dynamics of the personalized-medicine market. We will examine the economics of each step along the development pathway and suggest policies to control costs across the product lifecycle.

This analysis encompasses all aspects of clinical development and product marketing. Specifically, we will examine the cost of drug development in personalized medicine, cost of capital for product development, target market size, marketing costs, returns to innovators at a product level, returns to innovators at a firm level, and, finally, product pricing. This examination will identify new initiatives that would support a more sustainable business model to encourage continued innovation in oncology.

COSTS OF CLINICAL DEVELOPMENT

The out-of-pocket costs of drug development are significant. In the seminal paper on the topic by DiMasi et al. from 2003, direct costs were estimated to account for $130 million of the $802 million (2000 U.S. dollars) that it would cost to develop and approve a new therapy.2 When this analysis was repeated for biopharmaceuticals in 2007, the costs estimate rose to $166 million and $1.2 billion (2005 U.S. dollars), respectively.3 This price tag is likely far higher today, driven by the complexities of developing and implementing clinical trials, including the central costs for the sponsor, the costs of data collection and analysis, the payments required to site investigators, the site expenses (e.g., laboratory, genomic and imaging studies), and the cost of trial committees such as those for adjudication and data safety monitoring.

Clinical trials are a resource-intense endeavor.4 There are many steps devoted to the identification of trial participants, to the screening of patients to identify those eligible to participate, to the fixed overhead required to recreate each trial from the ground up, to the development and monitoring of data collection, and to the hidden non-value-added costs within institutions such as overhead. At the Duke Clinical Research Institute, we are working to devise a new approach to the cost-prohibitive aspects of clinical research, leveraging mobile health and informatics technologies in the process. The goal is to streamline drug development, and reimagine the roles and responsibilities of both the patients and clinicians.

Patients with rare diseases such as chordoma are often engaged by patient advocacy organizations and enrolled in disease-specific registries of varying sophistication.

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Authors’ disclosures of potential conflicts of interest are found at the end of this article.

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The registries can be used to identify and approach potential participants for clinical trials, but this function is vastly underutilized. In conjunction with advocacy groups, a registry framework is being built wherein trial start-up, recruitment, monitoring, genetic analyses, support of randomization in routine practice, and other needs, could be automated and monitored in aggregate. Novel technologies should play a larger role in the conduct of clinical research, including the aggregation of data about the patient experience across geographies and populations, the collection of symptoms and quality-of-life data, the documentation of adverse events, and the capture of robust treatment information in real-time directly from the patient and clinicians. In this process, the traditional medical establishment can be circumvented, going directly to patients and streamlining the process.

Critical pieces of the clinical trial process can be augmented or replaced. Start-up times can be drastically reduced because a national cohort of patients interested in participating has been identified before approval of the study. Recruitment goals will be far easier to attain, as enrollment will no longer be dependent on site-based patient identification during clinical visits. Aspects of follow-up can be automated, not requiring the patient to be seen. The data provided can be supplemented with informatics-enabled conduits from electronic health records to automatically populate aspects of the registry systems. Biobanks can be clinically annotated using the registry system, providing ready access to tissue. In the end, our hope is that the direct cost of drug development could be drastically reduced.

**COST OF CAPITAL**

The costs of drug development include the cost of financing the out-of-pocket cash outlays for the development program (clinical trials) and the time costs of development programs that can span a decade or more. These costs are referred to as the cost of capital. The longer the delay between cash being expended and revenues being generated, the more the expended cash would be worth in today’s dollars and, by extension, the higher the cost of capital. In the original Grabowski model, the cost of capital increased the cost of preclinical and clinical development from $169 million to $375 million. Three real costs to firms, both in supporting the capital allocation as well as in “opportunity costs” that come from not pursuing other investment opportunities. The cost of drug development can be reduced by envisioning new ways to decrease the time required for clinical trials to be completed and to decrease the cash outlays required of sponsors.

In a recently published illustration of this concept, Valverde et al. outlined a new approach to drug development for rare diseases that they called the “Grant-and-Access” program. Despite the Orphan Drug Act of 1983, many rare diseases have few treatment options and those treatments that have been developed are exceedingly expensive. The authors proposed an approach in which federal grants are used to subsidize the direct cost of clinical drug development. In return for this financial assistance, sponsors for the agent being developed would agree to a cap on the price that is ultimately charged on the basis of a rate of return model in which a prespecified return on their investment would be guaranteed if the agent is approved. The concept of accelerating development by reducing the cost of capital has already expanded well beyond this initial example. Organizations like the Gates Foundation provide grants for promising research ventures to decrease the cost of development and ensure that innovation moves forward in an accessible fashion. One could foresee a path in which the patient advocacy groups who are reimagining the research enterprise would also help fund promising product development to decrease the capital costs for sponsors.

Another approach to addressing the cost of capital issue would be to envision a system based on conditional approval as a core construct. Accelerated approval has been common in oncology in which agents are preliminary approved for marketing on the basis of surrogate markers such as progression-free survival for particularly serious diseases with few alternative treatments. Final approval is contingent on confirmation of the efficacy of the drug on further study. Conditional approval shares the same premise; however, it differs from accelerated approval in that it allows for a development strategy consisting of smaller phase III trial programs with significant postmarket requirements on safety and efficacy. An agent is withdrawn from the market if safety or efficacy end points are not met at any point in the development pathway. This approach directly addresses concerns about the cost of capital in two ways: (1) it decreases the direct costs of clinical trials, and thus the capital required for the initial development by decreasing the size of preapproval trials; and (2) it decreases the time from trial initiation to approval and allows the generation of revenues earlier in the process, decreasing the time costs of drug development.

**KEY POINTS**

- The concept of personalized medicine is beginning to come to fruition, but the cost of drug development is untenable today.
- There are no good mechanisms immediately available to address the costs as we seem to have all but abandoned traditional strategies such as the use of cost-effectiveness analyses to drive decisions.
- The economics of drug development must therefore be re-envisioned, including the cost of drug development, cost of capital, target market size, returns to innovators at the product and firm levels, and product pricing.
- Examples of novel approaches include leveraging technology and patient advocacy groups to lower trial costs, using grant support and approval pathways to decrease the cost of capital, and relying on preclinical biomarker development to increase the success rates of new agents.
- Although a quick fix is not available, a rethinking of the entire pharmaceutical development process is very promising.
TARGET MARKET SIZE
As personalized medicine gains traction and biomarkers are developed alongside novel agents, the market size for targeted therapies may be smaller because of market segmentation. Market segmentation occurs when, instead of broadly marketing an agent, its use is limited only to those patients with a given biomarker that predicts a high likelihood of response and/or a low likelihood of adverse events. As examples, testing for KRAS mutations before the use of cetuximab (Erbitux, Bristol Myers Squibb, Princeton, New Jersey, USA) in patients with colorectal cancer or HER2/neu testing before the use of trastuzumab (Herceptin, Genentech/Roche; San Francisco, CA, USA) in patients with breast cancer, targets the agents only to those patients most likely to benefit. To date, sponsors have compensated for this decrease in market size through higher pricing.

Biomarkers may decrease the potential market size for an agent, however patients who are positive for the biomarker are more likely to receive the agent and to respond to it. The economic balance of these competing factors is largely dependent on the nature of the available treatments for a given cancer type. If there are numerous previously approved options, a companion diagnostic may carve out a niche and increase revenues. In those with few available options, it might limit the market beyond what would otherwise be achieved.

Regardless of the situation, there are ways in which biomarkers could be beneficial. Their use will further decrease the out-of-pocket costs by decreasing trial size and duration, thereby decreasing the cost of development. The identification of biomarkers in preclinical and early-phase trials enables the efficacy of an agent to become more pronounced and for a targeted patient population to be enrolled. A prior review by Ginsburg et al. further highlighted ways in which genomic signatures may increase productivity of drug development such as by guiding dose adjustments. A separate analysis estimated that the integration of genomics into preclinical testing may result in a decrease by “20% in the number of new compounds in phase II trials, by 10% in the number of patients in phase III trials, and by 20% in the length of phase III trials.” The overall result could be to decrease the number of failures and further streamline clinical development.

A smaller market size could also provide a benefit in marketing the agent, thereby lowering costs while maintaining higher market penetration. Marketing expenses, especially to support pharmaceutical representatives, account for a significant percentage of overall pharmaceutical industry costs. As a result of rising concerns about expenditures and legislative changes regarding the role of pharmaceutical representatives, the ability to market novel agents is changing quickly. As market segmentation increases, the target patient population shrinks and new approaches to the marketing of agents, relying on social media and patient advocacy groups, will be powerful. In oncology, imagine if instead of trying to use current advertising and representative-based means to reach the entire colorectal cancer population, one can target, through social media and advocates, those with particular demographics and clinical characteristics known to predict the presence of a biomarker of interest, making the marketing campaign more efficient and far less expensive.

RETURNS TO INNOVATORS AT A FIRM LEVEL
In the previously referenced paper by DiMasi et al., a large portion of the $1.2 billion price tag for each approved molecule is related to the rate of failure of agents. Only 30% of all biotechnology products that are brought into development, and 19% of monoclonal antibodies, are ultimately approved by the United States Food and Drug Administration. The costs of agents that fail are ultimately borne by sponsors. Increasing the likelihood of success would thereby decrease the overall cost of drug development.

To address the rate of failure and the productivity of drug development, the overall approach of the pharmaceutical industry must be reconsidered. At present, profits are driven by a few blockbuster agents, which generate outsized returns for sponsors. In the current model, the required return on investment is dependent on only a few agents. If the development process and cost of capital are reformed as outlined, the same research and development budget could support more clinical development efforts and ultimately lead to more products that are approved and marketed. This increase in productivity could reduce the pricing pressure for each new product since overall returns at the firm level would be based on sales of more products in their portfolio. As Bernard Munos explained to Forbes in 2011, “instead of chasing improvements to blockbuster drugs that help lots of people a little bit we should focus on true breakthroughs that help patients a lot…companies should close their labs and outsource the work to tiny, nimble startups that can explore bigger crazier ideas.” These comments were based on his findings that the share of new drugs (new molecular entities) that came from large pharmaceutical companies dropped from 75% in the 1980s to 35% by 2004 while those of small biotechnology and pharmaceutical companies increased from 23% to 70%.

Having a robust portfolio of products will distribute the costs of development, making all more affordable. As described previously, a first step would be to use genomic signatures to target drugs to high-risk populations in which it might be easier to assess efficacy and decrease the number of compounds that fail in phase II and III testing.

RETURNS TO INNOVATORS AT A PRODUCT LEVEL AND PRODUCT PRICING
In the end, this all leads back to the topic of pharmaceutical pricing for new products, focusing particularly on personalized medicine products. The financial considerations impacting the development of pricing strategies for pharmaceutical companies should not be oversimplified. There are many costs to drug development that complicate pricing decisions and each must be considered and addressed. We propose...
that there are emerging paradigms that could transform the pharmaceutical development framework that need to be further explored.

Consideration must also be given to broader policy issues in the United States regarding market efficiency for personalized medicine products. Even if significant savings are achieved in areas such as out-of-pocket costs and the cost of capital, they would not necessarily be passed on to the consumer through pricing changes. One recent paper suggests that the lack of price elasticity in the U.S. market is a unique feature of the insurance market in the United States. If this is the case, we might need to develop better frameworks to allow insurance companies to have more leverage in reimbursement negotiations with sponsors.

**CONCLUSION**

There are numerous approaches that could fundamentally alter the economics of drug development, thereby allowing for innovation and progress in common diseases. Many of these are ongoing today. Patient advocacy groups and advances in technology are paving the way to address out-of-pocket costs for clinical trials. Grant support and accelerated/conditional approval pathways have the potential to decrease the cost of capital. Biomarkers will segment the market, allowing new approaches to marketing, and will increase the productivity of drug development, decreasing the number of failures among agents in clinical trials. Pharmaceutical companies should reimagine their drug-development pipeline to be more nimble. New policy approaches could replace monopolistic pricing with measured approaches tied to returns on investments. In aggregate, the opportunities abound.

Although many of the concepts we have developed are potentially transformative, they will not address issues with the pricing strategy of the agents currently on the market. Unfortunately, there are few good mechanisms that are immediately available. We seem to have all but abandoned an evaluation strategy that relies on cost-effectiveness. Clinicians and patients have routinely equated any discussions of cost and value to “rationing” and ended discussions abruptly. The widespread use of tieredformularies and cost-sharing efforts focused on the patient are equally problematic. These approaches rely on the theory of moral hazard. Consumers are thought to use greater quantities of a product if they do not directly endure any risk. Through the use of copays and other mechanisms, patients could be forced to have “skin in the game” and thereby encouraged to choose only those treatments that are truly needed. In oncology, we posit that the theory of moral hazard is less relevant. Prospect theory is a behavioral economic theory arguing that people make decisions related to the magnitude of potential losses and gains. Although cost sharing may allow the avoidance of marginal services among the healthy (addressing moral hazard), the potential substantial risk of death related to a cancer diagnosis makes cost sharing less effective and limits the potential role of market forces (prospect theory). If you can imagine someone in good health making a decision about whether to fill a $5 prescription for pain, cost sharing may provide an appropriate influence. On the other hand, a patient with cancer who is told that he or she is likely to die within a few months is willing to risk nearly anything to get their treatment. Unfortunately, the result of prospect is observed in data showing the high rates of bankruptcy in the population of patients with cancer in the United States. For these and other reasons, a quick fix is not available. Instead, a rethinking of the entire pharmaceutical development process is critical.

**Disclosures of Potential Conflicts of Interest**

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**Employment or Leadership Position:** Kevin A. Schulman, Cancer Consultants (U); Faculty Connection (U). **Consultant or Advisory Role:** Kevin A. Schulman, Ainylam. **Stock Ownership:** Kevin A. Schulman, Ainylam. **Honoraria:** None. **Research Funding:** Kevin A. Schulman, Ainylam. Bradford R. Hirsch, Bristol-Myers Squibb; Pfizer. **Expert Testimony:** None. **Other Remuneration:** None.

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