Published in final edited form as:
J Investig Med. 2012 October ; 60(7): 995–998. doi:10.231/JIM.0b013e318268694f.

TRANSLATIONAL RESEARCH AND THE EVOLVING LANDSCAPE FOR BIOMEDICAL INNOVATION

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Abstract

This article addresses current challenges facing pharmaceutical and biopharmaceutical developers, including the expiration of patents on many high revenue generating products, increasing competition of the marketplace, low public support, high regulatory hurdles, and the increasing time, cost, and risk of new product development. To meet these challenges, drug developers are looking to new models of innovation to improve efficiency, lower risk, and increase output. These new models include co-development agreements with small companies, multi-company consortia, and strategic partnerships with academic research centers. In the United States and the European Union, the government is supporting these efforts by creating incentives for academic centers to foster translational research and become more "commercially minded". The goal for all stakeholders is to reduce the barriers to product development and bring new medicines to market in a timely and cost-efficient manner.

PHRASES

biomedical innovation; translational research; drug development; academic research centers; drug industry; current challenges; FDA; NIH

INTRODUCTION

Over the past decade, translational research has become a significant topic of discussion and a driver of change within academic institutions, government research centers, and the biomedical products industry. Many organizations now have dedicated departments to support and promote the objectives of translation research. Despite the near ubiquitous use of the term, however, translational research is often ill defined or misunderstood.

Translational research is typically described as a process for facilitating the movement of new medical therapies from "bench to bedside." "Bench," or basic research, often occurs at academic or government research centers. "Bedside," or use of new therapies to affect

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Disclosures

The Tufts Center for the Study of Drug Development (CSDD) is a nonprofit, academic research center at Tufts University School of Medicine, Boston, MA, USA. Tufts CSDD is funded in part by unrestricted grants from pharmaceutical and biotechnology firms, as well as companies that provide related services (e.g., contract research, consulting, and technology firms) to the research-based industry.

The following manuscript is adapted from Dr. Kaitin's presentation at the AFMR Translational Research Workshop in Washington, D.C., on April 9, 2011

The author reports no potential conflicts of interest relevant to this report.

disease processes and patient care, is a clinical practice issue. But what happens in the middle stage, between bench and bedside? In this article, derived from a presentation given at the American Federation for Medical Research (AFMR) translational research workshop, I will focus on the stages of development that represent how over 95% of approved prescription drugs reach the pharmacy shelf. In other words, I will present bench-to-bedside, with a stopover in industry, for a look at how commercialization of those products occurs.

To highlight the challenges of bringing a new pharmaceutical product to market, I will present data collected and analyzed by the Tufts Center for the Study of Drug Development (CSDD). Tufts CSDD, which I direct, is an academic, multidisciplinary research group based at the Tufts University School of Medicine. Founded in 1976, Tufts CSDD is committed to providing strategic information to help drug developers, regulators, and policy makers improve the efficiency of pharmaceutical innovation. The research faculty of Tufts CSDD focuses on the economic, legal, political, and regulatory issues that affect the development and regulation of pharmaceutical and biopharmaceutical products. In addition, Tufts CSDD publishes metrics on the drug development process, which I will share in this document.

In this article, I will present some of the challenges that are changing the environment for pharmaceutical innovation, and how academic–industry partnerships represent a new and evolving model of biomedical innovation.

CHALLENGES FOR PHARMACEUTICAL DEVELOPERS

These are challenging times for the research-based drug industry. A major concern for many companies is the relatively large number of patents on many top-selling medicines that have recently expired, or will soon expire.[1] Because companies typically rely on relatively few products in their marketed portfolio to generate the revenues to sustain their R&D efforts, and since many of these products are the ones losing patent protection, companies must either substantially increase the number of new products reaching the marketplace to replace those that have gone off patent, or dramatically reduce R&D expenditures. Several of the larger companies have recently announced plans to significantly cut their spending on R&D, while boosting their efforts to bring more products to market.

Another challenge for the industry is that the pharmaceutical marketplace has become increasingly competitive, making it more difficult than ever to get the premium pricing and the kind of formulary coverage that most companies seek for their products.[2] Companies can no longer simply develop products that are just “safe and effective”; they must develop products that are also cost effective, to compete in the market. This competitive pressure is growing, especially in the United States, as evidenced by the creation of the Patient Centered Outcomes Research Institute (PCORI) and the increasing focus on comparative effectiveness research (CER).

Other challenges for the industry include an increase in regulatory hurdles in major markets, especially in the areas of safety assessments, risk management, and post-approval research requirements. In addition, public support for the pharmaceutical industry has been, and continues to be lacking, which has a corrosive effect on a company’s “brand.”

Ultimately, however, perhaps the greatest challenge facing the industry is the one issue that companies have a substantial amount of control over – the R&D process itself, that is, the time, cost, and risk of developing new products. Despite nearly two decades of intense effort to speed development times, decrease attrition rates, and reduce overall costs, drug developers have made very little headway in improving the drug development process.[3]

PHARMACEUTICAL R&D—A LONG, RISKY, AND EXPENSIVE PROCESS

The new drug development process—the process of bringing a new drug candidate through the product development process, gaining regulatory approval, and launching into the marketplace—can be viewed metaphorically as a funnel. The many candidates generated in early stage discovery research enter the funnel at the wide end, and move through a selection process, which includes identifying viable targets for development (i.e., 'target identification') and selecting the optimal molecular characteristics of lead candidates for further development (i.e., 'lead optimization'). The overall number of candidates is quickly whittled down, until a smaller number eventually reach the preclinical, or animal testing phase, to assess safety in an animal model and learn about the pharmacokinetic properties of the candidate. For those candidates determined to be worthy of further development, an investigational new drug application (IND) is filed with the FDA by the sponsor, which signals the sponsor's intention to enter the clinical testing phase and begin studying the candidate in human subjects.

Clinical testing includes phases I, II, and III, in which the safety and efficacy of the candidate is assessed. Eventually, the sponsor may submit a new drug application (NDA) or a new biologics application (NBA) with the FDA. The NDA/NBA is reviewed to determine whether the benefits of the candidate outweigh its risks. If approval is granted, the FDA may still require phase IV studies to assess long-term safety and effectiveness. In recent years, 80% of products that have been approved have been required by the FDA to undergo post-approval studies, post-marketing surveillance, and life-cycle management.[4] Life-cycle management includes studies conducted to assess new uses for the drug. The product development process from synthesis to regulatory approval may take as long as 15 years.

DRUG DEVELOPMENT METRICS: TIME, RISK, AND COST

The focus of much of industry's attention is an unwieldy drug development process, which remains stubbornly risky, time-consuming, and expensive. In the United States, R&D spending on new pharmaceuticals continues to spiral upward, exceeding $65 billion in 2010. At the same time, the number of new molecular and biological entities approved by the FDA remains relatively low. The persistent low number of new molecular entities approved by the FDA, in light of the huge R&D investment by the research-based industry, is viewed by some as symptomatic of a faulty business model within the research-based sector.[5]

Based on recently published data by Tufts CSDD,[6] the average capitalized cost to bring one new biopharmaceutical product to market, including the cost of failures, is $1.2 billion, in 2005 dollars. For traditional pharmaceutical development, the cost is $1.3 billion per approved product. These costs reflect the difficulty of developing products for ever more chronic and complex indications, for example neurologic and immunologic diseases, the rapid growth in the size of clinical studies, the difficulty recruiting and retaining subjects for these studies, and late stage failures in the drug development process.

Current Tufts CSDD data indicate that the average time to bring a pharmaceutical product to market, from synthesis to marketing approval, is about 15 years, approximately seven of which is spent in the clinical testing and regulatory approval stages of development.[7] Moreover, the likelihood of clinical success is a dismal 16%.[8] Of course, these numbers mask considerable variability across different therapeutic areas. For example, the time from the start of clinical testing to submission of an NDA in the United States ranges from 4.6 years for AIDS antiviral drugs to 8.1 years for drugs to treat central nervous system (CNS) diseases and disorders. Similarly, overall clinical approval success rates, that is, the likelihood that a candidate starting clinical testing will eventually be approved for

marketing, ranges from 23.9% for systemic anti-infective agents to an exceedingly low 8.2% for CNS drugs.

REASONS FOR THE RISE IN DEVELOPMENT TIMES AND COSTS

The time, cost, and risk involved in bringing a new drug to market represent formidable obstacles for pharmaceutical developers. The reasons are varied and multifaceted. For example, industry's focus on more chronic and complex indications has led to profound growth in the size and complexity of clinical trials. Adding to the difficulties is the increasing challenge of recruiting and retaining study subjects, more stringent regulatory demands, especially in the area of safety, more market-oriented studies necessary to ensure payer reimbursement, and the high cost of some of the popular research and discovery tools, such as high-throughput screening, combinatorial chemistry, and pharmacogenomics, that many companies are using to increase the number of potential development candidates.

THE FUTURE OF R&D: FROM CHALLENGE TO CHANGE

To remain competitive in today's pharmaceutical marketplace, many drug firms are focusing on operational improvements in the product development process, as well as on the adoption of new R&D strategies to position the company for sustained growth and success. Within the area of operational improvement of the drug development process, some companies have established specific performance goals. These include increasing the number of products in the pipeline, cutting discovery and development timelines, reducing late-stage failures, containing R&D costs, increasing overall output, and focusing on breakthrough therapies. To achieve these goals, companies are working to eliminate waste and redundancy in the drug development process, establish a global development organization, create a strategic approach to in- and outsourcing, utilize adaptive and enhanced clinical trial designs, increase the use of new data management technologies and eR&D, and engage in substantive interactions with global regulatory agencies.[9]

In terms of new R&D strategies, some companies have looked to mergers and acquisitions, while some have engaged in R&D reorganization, especially to create smaller, more autonomous research units. In addition, many companies are focusing on new forms of partnerships, in particular with academic institutions. There are also an increasing number of risk-sharing relationships among companies, for example, between large and small firms, or through the creation of consortia. Finally, some companies are re-assessing R&D strategies that focus on large-market indications, and are moving toward smaller, niche pharmaceutical markets, where therapeutic need is great, competition is decreased, and return on investment may be substantial.

A major shift within the commercial sector is the transformation from fully-integrated pharmaceutical companies (FIPCos, i.e., companies that can take a drug candidate from laboratory bench to market) to a network model that encompasses all the major stakeholders in drug development, including large and small pharmaceutical and biopharmaceutical firms, academic research centers (ARCs), patient groups, public-private-partnerships, and contract research organizations (CROs).[10] In the new model of innovation, all these stakeholders will have a place at the table, and will share in the risks and the rewards of innovation.

Ultimately, new drugs and biologics may emanate from "innovation nodes." Innovation nodes will be disease- or therapeutic area-focused, and they will allow developers to leverage the capabilities and expertise of the participating stakeholders.[11]

ACADEMIC-INDUSTRY PARTNERSHIPS

Key to this new, integrated model of innovation is the relationship between pharmaceutical companies and academic institutions.[12] Enabling factors include the necessity of some of the larger pharmaceutical companies to make significant cuts in R&D spending, as well as the need of many ARCs to find new revenue streams in light of the paucity of available National Institutes of Health (NIH) funding. Moreover, these efforts have received the support of governments. During the past decade, the United States and the European Union (EU) have developed programs to foster translational science.[13] For example, in 2001, the U.S. NIH released its NIH Roadmap,[14] which was intended to invest in new pathways in drug discovery, support research teams of the future, and re-engineer the clinical research enterprise. In 2006, the Clinical and Translational Science Award (CTSA) program,[15] which was intended to facilitate the transfer of knowledge between basic research and clinical medicine, was launched. With approximately 60 CTSAs awarded to date, the NIH has clearly signaled its support for academic institutions as active partners in bioinnovation.

In a similar vein, in 2004, FDA introduced the Critical Path Initiative (CPI)[16] to improve the translation of basic research findings into safe and effective medicines. Mirroring the goals of the EU Innovative Medicines Initiative,[17] a public–private partnership formed in 2007 between the European Federation of Pharmaceutical Industries and Associations and the European Community, CPI fosters precompetitive research by bringing together the respective capabilities of academia, industry, and government to identify new biomarkers and other tools to improve the selection of drug candidates and increase the likelihood of pipeline success.

Despite a shared commitment by both industry and academia, and the unequivocal support of government, significant obstacles stand in the way of successful partnerships. These obstacles include language barriers (academics speak the language of science while industry speaks the language of business), misaligned reward systems (academics are rewarded for research and publication through promotion and grants, while industry employees are rewarded for pipeline success and regulatory filings through bonuses, promotion, and meeting company goals), intellectual-property issues (academics try to retain ownership as much as possible while industry requires sufficient rights to make downstream investment worthwhile), and a heightened sensitivity to conflicts of interest in academics and a reluctance to align too closely with the private sector.[12]

Nonetheless, there are many reasons to be encouraged about the opportunities created by academic–industry partnerships. In particular, industry gains access to cutting-edge science and new technologies, and academics gain access to drug development expertise and an increased likelihood that their research discoveries will ultimately result in new treatments and medicines. Moreover, academic-industry partnerships represent the key to seeing the fulfillment of the ultimate objectives of translational science.

CONCLUSIONS

Unprecedented challenges confront pharmaceutical and biopharmaceutical companies in their quest to bring innovative new medicines to market. Rapidly growing R&D costs, increasing competitive pressures, an uncertain regulatory environment, and a highly volatile public and political climate represent significant threats to the research-based industry.

We are in a period of dynamic change in the innovation landscape. In the new environment, innovative medicines will likely result from the combined efforts of numerous stakeholders – including large and small pharmaceutical and biotechnology companies, ARCs, patient groups, CROs, and public-private-partnerships.

Acknowledgments

The American Federation for Medical Research Symposium was supported in part by a grant from the National Center for Research Resources (R13 RR023236)".

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