Twenty-First Century Pharmaceutical Development

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Introduction

Peter Blaisdell

The past century has seen a phenomenal application of advances in basic science for the development of pharmaceuticals, diagnostics, and medical devices. However, this will pale relative to the advances that will occur in the twenty-first century as further progress is made in understanding molecular biology and physiology. One manifestation of this progress is the sequencing of the entire human genome. In combination with continued progress in understanding gene expression and function, this will create new opportunities for diagnosis and therapeutic intervention. Morbidity and mortality associated with cancer, cardiovascular disease, infections, diabetes, and aging itself will become ever more amen-able to treatment.

Facilitating the commercialization of scientific discoveries has been the evolution of a process for drug development over the past several decades. This process includes activities leading from the research lab to a marketable product. In coming decades, the development process will be influenced by several factors, including the standardization of government regulations controlling drug development across the major markets for pharmaceuticals—North America, Europe, and Japan. South America, China, and other parts of Asia will probably adopt similar regulations to create a relatively homogeneous global environment for therapeutic development within the next decade or two. Further, these same governments are likely to insist on becoming even more involved than they currently are in controlling drug costs to consumers. This will challenge the pharmaceutical industry to develop pricing strategies that can survive government scrutiny while preserving enough corporate profits to fund the expensive and uncertain pharmaceutical research process.

Future drug development will also be influenced by the continued consolidation of global pharmaceutical businesses into ever-larger entities. Currently, no one corporation controls even 10 percent of the total pharmaceutical market. However, this will likely change as large players merge.

Increased size will allow for efficiencies in the marketing, manufacturing, and regulatory efforts needed to launch a new drug globally. Whether size alone will also lead to efficiencies in the pharmaceutical research effort remains to be seen. Certainly, in the later twentieth century, some small biotechnology firms proved adept at exploiting basic biological research on shoestring budgets by narrowly focusing on developing products for a single therapeutic area and outsourcing parts of the development effort. Whether such small companies continue to play an important role in developing drugs will be a critical factor in defining how pharmaceuticals are developed in coming decades.

This book, *Twenty-First Century Pharmaceutical Development*, provides an overview of how key aspects of the drug development process currently work and how they may be done in the future. The book is organized generally to reflect the various functional disciplines involved in the development of drugs, with chapters describing each of these areas. Clearly, some disciplines, such as basic research, are likely to experience great changes in the next few decades, but all functional areas are evolving as the advances in basic science allow fundamental health issues to be addressed.

The first chapter reviews financing strategies with a particular emphasis on issues critical for smaller drug companies. Creating therapeutics takes piles of cash; developing a drug from the basic research phase through international market launch may cost several hundred million dollars. Medical devices and diagnostics are usually less expensive than drugs, since they can require fewer clinical studies to confirm their safety and efficacy, but they, too, are costly to bring to market. For large drug developers, funding for future therapies is derived from current product profits. However, for smaller firms, with innovative technologies but modest financial resources, amassing the money needed to undertake the development process is critically dependent on external sources of funding. In the last 20 years, there have been mechanisms for providing such funding including venture capital firms (many with addresses on Sand Hill Road in Menlo Park, Calif.) willing to finance small pharmaceutical companies in return for high rates of return. By necessity, these sources of funding have had to be quite risk tolerant, as many drug development efforts fail. Because small pharma has been adept at converting cutting edge technology into new products—in many cases, more adept than large multinational drug companies—the accessibility of financing has been a key factor in growing the pharmaceutical sector. However, it is uncertain whether small drug firms can continue to avail themselves of such funding in the twenty-first century given competing opportunities in other, less heavily regulated technology sectors such as computer and communications development that offer faster returns on an investment. The chapter on financing reviews strategies to generate financing in this changing environment.

The core of pharmaceutical development is research, both at the discovery phase when new therapeutics are being identified and at the preclinical and clinical phases when the new therapeutics are assessed in animals and humans for safety and efficacy. *Twenty-First Century Pharmaceutical Devel-*

opment therefore devotes extensive chapters to each of these phases. The chapter on discovery research describes several current approaches to identifying genes of interest and their functions. This chapter also explores current methodologies for rapidly screening new leads for therapeutic utility against human diseases. An overview of gene therapy is also provided. Managing research efficiently without stifling creativity will be a central challenge in the new century.

Once a potential new product has shown promise during the initial screening process, it will be further tested in appropriate animal species to gauge its utility and safety in humans. The chapter on preclinical research provides an overview of both the current battery of animal trials used to determine a new lead compound's toxicology profile as well as describing promising new in vitro and in vivo methods that may replace or at least reduce the need for traditional safety testing in animals. If proven successful, these new methods have the potential to reduce both the cost and time needed for this stage of the development process.

The chapter on clinical research focuses on developing and implementing a clinical strategy that is consistent with overall corporate goals. It presents a detailed template to assist in aligning the development of a clinical program with the desired label claims and existing knowledge about the potential product's preclinical characteristics. Tools such as this will likely become more common as pharmaceutical firms struggle to balance speed of development with the need to conduct high-quality studies.

No description of the research phase of the drug development process would be complete without a description of the role applied statistics plays in clinical trial design. Thus, a chapter on biostatistics is included in this book to provide a statistical perspective on trial structure, inclusion of control groups, randomization, and sizing a study.

In concert with research activities to discover and develop a promising therapeutic, a pharmaceutical firm must also implement effective legal, marketing, and regulatory strategies. A chapter describes each of these specialties. Very early in the development process, the patent position of the promising new lead must be confirmed. The characteristics of patents are described in the chapter on intellectual property along with an overview of infringement and inventorship. The chapter also discusses how a robust intellectual property strategy will contribute to competitive advantage in the new century. Likewise, a clear regulatory strategy is critical in efficiently developing a new pharmaceutical product. The chapter on the regulatory process summarizes both the current Investigational New Drug/New Drug Application (IND/NDA) process as well as evolving trends toward paperless submissions, increased use of the internet to facilitate communications between the sponsor and the agency, and the efforts to harmonize regulatory standards globally.

Without a clear sense of the market for a potential product, the best drug development effort will be of limited value, producing a therapeutic or device that is not aligned with a patient population's needs. As described in the

chapter on selling pharmaceuticals, the traditional four P's of marketing—product, place, price, and promotion—are critical in selling drugs today and will continue to be important in the foreseeable future. However, understanding new factors affecting the twenty-first century pharmaceutical market will also be critical. One trend already well underway will be the aging of populations in the largest current markets, North America, Europe, and Japan, resulting in shifts in the types of therapeutics demanded by these consumers, most of whom receive medical payment support from their respective governments. However, therapeutic needs will also grow in younger but less affluent developing markets. In conjunction with these trends will almost certainly be increased efforts by governments and private healthcare providers to contain therapeutic costs. Another trend affecting drug marketing will be the Internet's role in supplementing established means of communicating a product's benefits to the target population as well as facilitating the dialogue between the pharmaceutical manufacturer and the patient. Clearly, the already intricate process of selling pharmaceuticals will become more complex in the new century.

Producing a drug in the form and quantity needed is, of course, essential. Therefore, two chapters describe the functions of formulation and manufacturing in the drug development process. Almost as soon as a potential new product is discovered, consideration needs to be given to an appropriate formulation - and the choices available are increasing. Traditional parenteral options including intravenous, subcutaneous, and intramuscular as well as liquid and solid oral formulations will continue to be important in many development efforts. However, new modes of formulation, including inhalation, transdermal, and other technologies, may offer more efficient means to deliver a given therapeutic. Formulations that can be targeted effectively may limit the "collateral damage" the patient incurs from the nonspecific effects of a given drug.

For a successful development effort, manufacturing should work closely with the formulation group. In addition to the classic challenges of scale-up and assuring consistency that pharmaceutical manufacturing has always faced with small molecules, the production of biopharmaceuticals will add further complexities as gene therapies need to be produced in large quantities. Of course, this will have to be accomplished in an increasingly heavily regulated environment.

A firm developing drugs or devices can outsource almost any part of the process from preclinical activities through marketing an approved product. Thus, a chapter is devoted to describing contract research organizations (CROs) and presenting factors that a sponsor needs to consider when deciding whether part or all of a developmental effort should be delegated to a CRO. Their use has become common over the last two decades for small and large pharmaceutical firms; despite skepticism on the part of sponsors, the next decade will likely see outsourcing continue as a critical part of development efforts. Drug and device makers are struggling to speed time to market

for new products while simultaneously containing costs. Outsourcing allows the sponsoring firm to avoid adding personnel and facilities while still undertaking many projects at the same time. A case study is also included to illustrate issues that are likely to arise between a sponsor and a CRO during a developmental project.

The activities of the many functional groups involved in developing new therapeutics are conveniently described as individual steps. *Twenty-First Century Pharmaceutical Development* takes this approach. However, pharmaceutical development should be conducted as an integrated team effort. In many drug firms, project management (or a functionally equivalent group) plays the critical role of coordinating activities of disparate groups who may have little appreciation of what their counterparts in other departments are doing. If portions of the project are being outsourced, the task of coordination becomes more complex as both internal and external resources must be meshed. By default, project managers must take a cross-disciplinary approach. Further, in an era of increasing time and budget constraints, project management will play a vital role in tracking and managing project schedules and costs. The chapter on project management describes this evolving role.

The bulk of *Twenty-First Century Pharmaceutical Development* focuses on the drug development process. Though similar in many overall aspects, diagnostic and medical device development are individual disciplines with unique approaches to regulatory, clinical, quality control, and manufacturing. An extensive chapter is devoted to both diagnostics and devices that describes their current development process as well as future trends.

The early decades of the twenty-first century will almost certainly see continued successes in turning basic biological research into exciting pharmaceutical products. Improvements in the drug development process described in this book will be critical in achieving this goal.

Peter Blaisdell, PhD
August 2000

About the Contributors

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Peter Blaisdell earned his PhD in biochemistry from the University of Minnesota where he also performed postdoctoral research. After completing his studies, he worked in the project management group at Quintiles, coordinating the activities of multifunctional teams developing pharmaceuticals for therapeutic areas including oncology, cardiology, and central nervous system disorders. He currently manages clinical studies in the Clinical Affairs Department of Amgen and teaches graduate courses in technology management at the University of Phoenix and San Francisco State University.

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