CHAPTER 1

INTRODUCTION

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The challenges faced by the pharmaceutical industry in the twenty-first century are potentially overwhelming. Nonetheless, there remains substantial demand for new medicines to address unmet medical needs. The global market for pharmaceuticals is growing. For cardiovascular, endocrine, metabolic, respiratory, neurological, infectious diseases, and oncology, the market is expected to exceed $500 billion by 2012.[1] The cost of drug development also is continuing to increase. The R&D expenditures for a single new chemical entity approach $1 billion.[2] Overall, attrition during drug discovery and development remains high. Thousands of compounds may be profiled before a development candidate emerges and only 1 or 2 in 10 that initiates testing in humans, is expected to reach the market.[3] The process overall may take 10–15 years. Despite R&D expenditures of $48 billion by Pharmaceutical Research and Manufacturers of America member companies in 2007, US drug approvals were the lowest in 24 years.[4]

Today, scientists in pharmaceutical R&D face unprecedented pressure from payers, regulators, ethicists, and the public, to bring to market safe and effective drugs while reducing costs. As recent events attest, even after having received regulatory approval, idiosyncratic drug reactions or infrequent adverse safety events may lead to "black-box" warning labels or potentially the removal of a drug from the market all together.[5,6] Serious adverse events may be extremely difficult to detect during the course of drug development given the numbers of patients

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involved in pivotal clinical trials and the relative homogeneity of these patient populations. Despite numerous challenges, sponsors need to anticipate the most likely asset profile, as early as possible, to make intelligent investment and portfolio decisions. Resource must be minimized for compounds less likely to progress through development. Given the increased costs associated with late phase development terminations, "fail early and fail cheap" has become the mantra for many in drug discovery.

Routine use of absorption, distribution, metabolism, and elimination (ADME) screening in drug discovery has successfully reduced attrition due to poor human pharmacokinetics from about half of all development failures in 1990,[7] to approximately 10% presently.[3] Experimental ADME screening remains a cost effective and robust way to assure a thorough understanding of the desired and undesired biological effects of a new chemical entity in animals and humans. For this, sufficient free drug concentrations must be maintained at the site of action, for an appropriate period of time, to enable a thorough evaluation of biological effects. This finding is as critical for comprehensive animal toxicology studies as it is for successful, decision-making clinical investigation.

This book describes powerful experimental approaches employed today by modern laboratories within pharmaceutical R&D, biotechnology companies, and academia to characterize ADME properties of drugs with a focus on small molecules. The primary *in vivo* and *in vitro* tools used to characterize a drug candidate are discussed. Included are theoretical and practical aspects of preclinical pharmacokinetics (in Chapter 2), the important role of transporters (Chapter 3) and the cytochromes P450 (Chapter 4), the role of metabolism and metabolite identification in drug discovery (Chapter 5), plasma protein binding (in Chapter 6), and the prediction of human pharmacokinetics (Chapter 7). Effort has been made to integrate the subject matter to account for important interdependencies. The concepts should be applied in a cross-functional manner and with due consideration of the context including potential clinical implications.

One of the most important sources of development termination today is animal safety. Our ability to predict toxicological effects of new drugs, particularly those that develop over time, continues to be limited due to the enormous complexity and dynamic nature of biological systems. Therefore, in conjunction with ADME, successful drug discovery depends on experimental toxicology. Chapters 9 and 10 of this book discuss general, genetic, and cardiovascular toxicology as it is applied in the drug discovery setting. Central to the field of

safety assessment is the consideration of the therapeutic window of a drug: the difference between exposure associated with the desired therapeutic benefit and exposure associated with adverse effects. Preferably, there is substantial separation between these drug exposures (a large therapeutic window) to permit safe and effective treatment for a heterogeneous patient population. The therapeutic window may decrease as the duration of dosing increases. Acute effects (desired and undesired) may differ from those observed with intermittent or chronic drug administration. The therapeutic window may or may not be conserved between preclinical species and humans (one reason to study multiple preclinical species). Different species may have different sensitivity to drug treatment (same effect at different exposures) or the biological effects themselves may differ from one species to another. The many challenges of early safety assessment include the provision of cost-effective *in vitro* and *in vivo* technologies that can be integrated into the drug discovery process and are predictive of clinical outcomes.

Additionally we included a chapter (Chapter 8) on pharmaceutics, encompassing theoretical and practical aspects of the physical characterization of drug substance, the importance of selecting an appropriate version (parent or salt) of the chemical for development and formulation considerations for definitive animal safety studies, and initial clinical trials. When fully integrated within a drug discovery program, drug metabolism and pharmacokinetics, safety assessment, and pharmaceutical development will play a crucial role. Together, they will assure the best chance of success by building the appropriate properties into the drug molecule as early as possible in the process. They will help to identify potential liabilities as the asset progresses, as well as areas for further specialized study. This is the nature of the developability assessment.

It is important not to underestimate the interrelatedness of these developability activities in drug discovery. Understanding and addressing issues at the interfaces can have a significant impact on the development plan, the time and resource involved in the activities, as well as the success of the program overall. For example, as previously indicated, animal safety studies will need to be performed to evaluate the full range of biologic effects including exaggerated pharmacology and off-target effects, acute and chronic, to appropriately manage potential liabilities. In many cases, prerequisites for this will include low to moderate *in vivo* clearance and acceptable oral bioavailability from a solid dosage form. This in turn will require well-characterized drug substance, a suitable formulation, and an understanding of

factors influencing the rate and extent of dissolution of drug at the absorption site.

Although some aspects of the process and strategy will be very similar from program to program, others will not. Development hurdles will differ depending on the therapeutic area, the availability of existing treatments, and ultimately the level of risk that may be acceptable given the potential benefit to the patient (the risk/benefit ratio). Therefore, the lead optimization strategy, including the staging of assays and the acceptance criteria will adjust accordingly. An analgesic or antibiotic may require relatively higher free drug concentrations thus rapid dissolution, high intestinal permeability, and low protein binding may be required. Some drugs will need to effectively penetrate the blood–brain barrier (e.g., an anticonvulsant). For other drugs, it may be desirable to have limited brain penetration. On this basis, assays to assess central nervous system (CNS) penetration may be included in the screening cascade.

Drugs administered intravenously will require relatively higher solubility and will need to have limited hemolytic potential. An asthma drug may be inhaled directly into the lungs and therefore relatively higher metabolic clearance may be desirable to minimize potential systemic effects. Others drugs will be used to treat a chronic condition (e.g., osteoporosis) and may be taken for many years on a regular basis. In this case, a longer biological half-life may be desirable. Some drugs will be taken in combination with others [e.g., antiretrovirals for human immunodeficiency virus (HIV) infection]. For these, it may be particularly important to study cytochrome P450 enzymology, to minimize the potential for drug–drug interactions. For diseases where there are limited or no therapeutic alternatives, convenience of administration will be less important. For life-threatening illnesses, there may be less of a concern regarding manageable side-effects, long-term or reproductive toxicities. Therefore, drug discovery strategy should be customized following thoughtful consideration of the desired product profile.

How does this complex process begin? In the earliest phase of drug discovery, a biological target (receptor, enzyme) is identified and its relationship to the disease process is elucidated. As confidence builds that inhibition of the target represents a valid approach for therapeutic intervention, assays are developed and a high-throughput screen is conducted. Libraries containing potentially millions of chemicals are tested for their ability to inhibit the target and hits are identified. When hits are deemed an appropriate starting point, lead optimization begins. During lead optimization, the structure of chemical leads is modified

to optimize potency, selectivity, cell-based activity, pharmaceutical, and ADME properties while assuring structural novelty that will form the basis of successful patent applications.

Patents provide market exclusivity for the innovator for a defined time period after which generic drug companies can manufacture and sell the same active ingredient. They must establish bioequivalence with the innovator's product (a statistical analysis of the rate and extent of absorption in humans). In so doing, they avoid conducting extensive clinical trials to evaluate safety and efficacy, which have been demonstrated previously by the innovator. The situation is more complicated for biologics since these products tend to be heterogeneous, and it is generally not possible to demonstrate chemical identity to the innovator's product. Regulatory agencies around the world are developing strategies for approval and marketing of well-characterized biologics given the potential for substantial savings and increased benefit to patients and society.

During lead optimization, a team of scientists including chemists, biologist, and drug metabolism and PK experts will work closely together to develop an appropriate screening cascade. This is a series of assays of various priority and throughput that are performed sequentially to optimize compound properties. Higher throughput assays designed to measure and incorporate the most critical attributes of the molecule are typically performed earlier in the screening cascade and require relatively smaller amounts of compound for testing. More detailed and resource intensive studies take place subsequently on a more limited number of promising compounds. These studies often require a larger quantity of drug for testing. It always requires some work to be performed in parallel, at risk, to avoid unnecessary delay. Turn-around time becomes critical in such a cascade because test results influence the subsequent round of chemical synthesis and biological testing, the order that compounds may be studied subsequently, and their priority for scale-up and further evaluation.

Assays with insufficient capacity to accommodate leads that have passed previous tests have the potential to become a bottleneck. Although assays may be redeveloped or resources redeployed to improve the situation (or acceptance criteria changed), bottlenecks often persist or may move to other areas within the screening cascade. Scientists involved in profiling compounds during lead optimization will require perseverance and creativity to adjust their experimental approaches to meet the needs of the program. Appropriate distinctions will be made between assays used for more definitive assessments and predictions, compared to those used primarily for rank ordering or

screening compounds. Thus, drug discovery assays will be fit for this purpose.

During lead optimization there will be occasions when a particular challenge presents itself and the team will need to pull together to address the challenge. Changes may need to be made in the screening cascade temporarily to solve a particular problem. Or, a parallel screening cascade may need to be put in place temporarily. Identifying and addressing these challenges will be critical for the success of the team, which requires strong leadership, excellent working relationships among team members, and thoughtful integration of data and information.

Various organizational models have proven successful in promoting collaboration and efficient decision making. In one model, the line functions [e.g., chemistry, biology, drug metabolism and pharmacokinetics, pharmaceutical development, and safety assessment] are separately managed. In this case, individuals are appointed to represent their discipline on a matrix program team and senior line management assures resources are aligned in a manner that is consistent with the overall strategic intent of the organization. In another model, smaller drug discovery units are dedicated to a therapeutic area or therapeutic approach and have, more or less, ring-fenced resource and potentially considerable autonomy. Typically, these drug discovery units include the minimal essential complement of scientists required considering the phase and maturity of the program (for lead optimization, often chemistry, biology, and DMPK). Ideally, these scientists are colocated to facilitate frequent discussion, interaction, and collaboration.

The former model may be more bureaucratic, accountability may be less clear, and loyalty may be split between the line function and the team. On the other hand, the larger line functions will likely have more specialized expertise and may be better able to respond to peaks and troughs in activity by reassigning staff to the most active and/or highest priority projects. In the latter model, the entrepreneurial model, there may be a greater sense of ownership, empowerment, and engagement. Of course, another model that has developed recently matches various aspects of the above with an aggressive outsourcing strategy. In this case, much of the laboratory work is performed by contract research organizations (CRO). More often than not, the CRO is located in a market where the cost of labor may be substantially lower than in the United States or western Europe.

In any case, it is inevitable that as teams advance compounds further into development, substantially more resource will be required and more discussion and debate will take place to assure organizational

consensus, as well as continued commitment to the project and the underlying development plans. Most teams will eventually require expertise and resource outside of their direct control and thus the importance of skilled matrix management and team work should not be underestimated. The most successful teams will take full advantage of expertise on and off the team, tapping into know-how and experience where ever it may exist. Transparency and communication will be critical as issues often arise within one area that have the potential to impact strategy and planning in another.

One of the major challenges discovery and development teams will face is to assure that there is an appropriate balance between what needs to be done now and what can be done later. The critical path must be well defined and there must be consensus around what activities are most essential in advancing the program to the next major decision point. What activities need to be completed when and at what cost? What activities can be postponed without affecting the critical path? What kinds of enabling activities need to be considered? What are the issues and risks associated with delaying a resource intensive study? What is the asset profile and how does it compare to the desired product profile? In a world of limited time and resource, these types of questions need to be considered proactively and on an on-going basis as new data and information become available.

On behalf of my co-editors, Dr. Chao Han and serial editor, Dr. Binghe Wang, I would like to take this opportunity to thank the contributing authors for sharing their considerable scholarly expertise, for their tireless effort preparing their contributions, and for their patience as this monograph was compiled. We hope our readers find this book to be relevant if not insightful and we wish you the best of fortune in your journey to bring important new medicines to patients.

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