
1

DRUG DISCOVERY AND EARLY DRUG DEVELOPMENT

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1.1 THE DRUG DISCOVERY AND DEVELOPMENT SCENE

1.1.1 Pharmaceutical Research and Development Challenges

Although it is common practice to envisage the launching of a therapeutic as a linear paradigm comprising a drug discovery phase gradually bridging into a development phase, it should be noted that such a process is rarely so straightforward. There are many potential intersecting paths to a successful new therapy, often involving a mixture of successive or concurrent intellectual, scientific, practical, commercial, regulatory, and other considerations among academia, industry, and government. However, for the purposes of the focus of this book, the road to therapeutic success is being presented generally as a linear continuum starting with drug discovery, continuing to drug development, then submission to regulatory agencies and approval, and ending with what is hopefully a high-quality medication that exhibits optimal safety and efficacy in the target population.

Given the achievements in the past several decades in our understanding of the underlying mechanisms of disease, huge technological advances, and the goal of optimizing monetary, staff, and time resources, it would be expected that in the ideal world, in recent years we should have been witnessing an increase in the availability of new and improved medicinal products. However, anyone involved in health care delivery is well aware that this is not the case. The past five years have witnessed a dramatic decline in the number of new drugs approved by the U.S. Food and Drug Administration (FDA) compared to a decade ago. Compared

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to the highs of 53 in 1996 and 39 in 1997, the numbers of new drugs approved by the FDA was 21 in 2003, a decade high of 36 in 2004, 20 in 2005, 22 in 2006, 19 in 2007 (the fewest in 24 years), 25 in 2008, and 26 in 2009. Concurrently, the costs to discover, develop, and register an approvable new drug is compelling, and has been escalating from about \$800 million in 2001 [1] to \$900 million in 2004 [2] to about \$1.3 billion today (comprising approximately \$425 million for nonclinical and \$850 for clinical development, although such estimates do vary, depending on the source material and analyses techniques), and the time from discovery to commercialization ranges from 10 to 15 years. The good news is that the average time for FDA approval has declined to an average of 1.1 years in 2005–2007 from around 2 years previously. With patent protection lasting for 20 years, at least in the United States, the time frame for profitability remains relatively narrow, although a patent-protected drug is generally highly profitable during this protected period. Following are some of the contemporary perspectives, challenges, and pressures inherent in the pharmaceutical industry that affect the timely availability of novel therapeutics.

Research and Development Challenges

- Research and development productivity has been declining.
- Late-stage pipelines have become relatively thin.
- Industry is tackling diseases of greater complexity [e.g., oncology and central nervous system (CNS) malfunctions such as Alzheimer's disease, Parkinson's disease, schizophrenia, and bipolar disease], necessitating complex clinical design protocols.
- No drug is perfectly safe or spectacularly efficacious at all doses.
- The concept of risk/benefit ratio is changing with the realization that the balance may not only be determined by dose, but that different patients may be more likely to gain the benefit, whereas others may be more prone to risk.
- Marketing pressures within pharmaceutical companies may be at odds with research and development goals, including risk/benefit analyses.
- Many companies are pulling potentially good drugs out of the pipeline because of regulatory agencies' diminished tolerance for side effects.

Business Perspectives

- Industry is struggling with greater scrutiny, patent expirations, major mergers, poor stock performance, thousands of layoffs, and thinning pipelines.
- Generic competition will eliminate \$67 billion annual revenues for U.S. pharmaceutical sales between 2007 and 2012; more than three dozen drugs will lose patent protection during this interval.
- Accordingly, the first annual revenue decline in four decades will occur between 2011 and 2012.

- New blockbusters are lacking to replace old ones such as Lipitor and Plavix. There remains a mindset by many organizations that only blockbusters are worth developing.
- However, blockbuster mentality restricts research direction and diversification.
- To remain competitive, drug companies must adjust to shifting market conditions (including enhanced standard of care), which may become altered during the course of drug development.

1.1.2 Attrition During Discovery and Development

It is thus well known that the odds of a new chemical entity (NCE) finding its way to becoming a successful therapeutic agent are extremely low. Only one in 5000 to 10,000 NCEs are approved and, in both the United States and Europe, approximately one in nine compounds that enter clinical development end up as approved products. Emerging data seem to indicate that the approval rate is somewhat higher for biopharmaceuticals than for small-molecule drugs. In the early 1990s, one of the main causes of this high attrition was pharmacokinetics and bioavailability (including problematic clinical drug–drug interactions); however, with the recent focus on the very early assessment of such characteristics (Chapter 2), these properties can be identified to a great extent prior to the first-in-human (FIH) study, resulting in early elimination of compounds unlikely to elicit undesirable absorption, distribution, metabolism, and excretion characteristics in patients. In the past several years, the principal reasons for attrition are generally in the following order: clinical efficacy > nonclinical toxicology > commercial > clinical safety > pharmacokinetics/bioavailability > cost of goods > formulation [2]. Success rates can vary with the therapeutic area: For those NCEs entering an FIH trial, the percentages that end up as marketed drugs are approximately 20% for cardiovascular, 16% for arthritis/pain and infectious diseases, and 5 to 8% for oncology and CNS malfunctions.

The chapters in this book are designed to aid in the determination of the most efficient and effective path to the FIH trial with NCEs that have a high likelihood of morphing into successful therapeutics. It should be noted that the mindset of reducing attrition in clinical development should be in place from the earliest stages of discovery, given that research, development (nonclinical and clinical), and marketing personnel should be aligned as early as possible in the discovery process. In this manner, all relevant disciplines can help create the animal pharmacology models best predictive of clinical efficacy, and later to design a proof-of-concept endpoint in the FIH study to provide evidence that the molecular target is being hit and that hitting such a target will elicit the anticipated physiological response [the exploratory investigational new drug (IND) approach to rapid attainment of such information is discussed in Chapter 11]. Early coordination among disciplines can also help reduce attrition by the early elimination of compounds with poor pharmaceutical properties (e.g., solubility; permeability),

insufficient chemical and metabolic stability, low bioavailability, potent enzyme inhibition or induction, mechanism-based toxicity, and other characteristics that would affect the clinical safety and efficacy of an NCE. Whether within a “big pharma” company, a smaller pharma/biotech organization, or a virtual company, strategic planning at all stages of discovery and development are critical, and can make or break a company (Chapter 13).

1.1.3 Corporate Strategy Perspectives

Given the extraordinary challenges and extensive commitment of time, financial, and human resources necessary to achieve marketing of a successful drug, the end result is usually a relatively profitable enterprise for the pharmaceutical company compared with many other industries. Such profitability is important, as it enables the industry to reinvest in research and development for those debilitating diseases that require improved therapies. The pharmaceutical industry has witnessed more major changes in the past century than, arguably, has any other major industry. This is probably because as we learn more about the causes and etiology of disease, which continue to remain elusive because of the complexities of normal and abnormal biological systems, adjustments must be made continuously based on our emerging understanding of the continuum between efficacy and safety. The basic principle of pharmacology (i.e., that no drug is perfectly safe and that safety is dose dependent), is sometimes overlooked by those intricately involved in the process. Despite all the knowledge we have accumulated, most contemporary therapies still alleviate disease symptoms rather than resulting in a cure of the target disease.

Although discrete pharmaceutical companies have been developing drugs for well more than a century, no optimal business model has emerged that would be predictive of success. With the numerous scientific, medical, marketing, financial, and regulatory pressures and challenges of recent years, some companies prescribe to the “bigger is better” philosophy, such as the recent megamergers of Pfizer and Wyeth, Merck and Schering-Plough, and Roche and Genentech; whether such consolidation results in industry stabilization remains to be determined. Other big pharma companies have been establishing relatively independent small research units that seem to mimic those in smaller biotech companies. Small to midsized pharmaceutical companies, virtual companies, and smaller biotech companies often try to develop new drug candidates through to successful proof of principle in humans, and then attempt to partner with a larger organization with more extensive clinical development and marketing muscle. The smaller the company, the more likely it is to exit product development early. Virtually all companies—small and large—utilize the services of contract research organizations (CROs) to supplement their programs, and this resource is discussed later in the chapter.

For companies of all sizes, it is critical to have a portfolio management strategy which is dependent on such considerations as the inherent size, research/

development/marketing staff skills, tolerance for risk, geography, corporate culture, and unfortunately, internal politics. Once a decision is made to embark on the development of an NCE, a plan is put in place that incorporates time lines through to the anticipated new drug application (NDA). There are numerous strategies that can comprise such a plan. One approach, which can be extremely useful, in particular for staff scientists within specific disciplines who may not be privy to the “big picture,” is to write the outline of the drug label first. Although this may seem to be counterintuitive, focusing on and writing the target therapeutic qualities of a medicinal product can help in the design of specific studies that will determine whether the NCE meets those qualities.

The development plan should comprise several go/no go decision points (e.g., proof of principle), which will help determine whether a program should continue to progress through several gates. Often, however, other problematic data may emerge that are outside the formal decision points. One of the most difficult decisions is the timing regarding when a development program should be terminated, based on emerging problematic safety, efficacy, and/or pharmacokinetic data. A development program will typically have one or more “champions” and several stakeholders from numerous disciplines who may rationalize why the drug candidate should continue along the development path instead of intaking the difficult decision to terminate the program. The basic paradigm will continue to comprise intense planning, strategic decision making, extensive research, long-term nonclinical safety, and clinical safety and efficacy studies, comprehensive data collection and statistical analyses, and relevant support programs. Whatever the strategy, it is ultimately the drug that speaks, and it is incumbent upon all those within large or small organizations and all contributing disciplines to conduct the most appropriate studies that will enable all relevant aspects of efficacy and safety to be uncovered. Small and large studies in all disciplines must be conducted based on sound scientific disciplines, to avoid “garbage in–garbage out” results with equivocal interpretation. One cannot force a drug candidate to exhibit properties that it does not possess.

In light of the perspectives noted above, a primary goal of the chapters that follow is to help guide those involved in the exciting field of pharmaceutical discovery and development to plan and conduct those studies beginning with lead optimization (discovery support), to early development, through to the FIH trial. The goal is to evaluate NCEs that have the greatest likelihood of leading to valuable therapeutics, and to develop strategies that will optimize what are often limited monetary, time, and human resources. Moving forward, it will be important to adjust the focus of the various disciplines as new advances in biomedical and genomic technologies emerge, and to determine which of these technologies are really useful in predicting human safety and efficacy, thereby affecting the drug development process. It must always be kept in mind that the ultimate goal in drug development is not the NDA submission process but the attainment of an approved NDA.

1.2 DRUG DISCOVERY

1.2.1 Target Identification

Drug discovery is a process whereby potential therapeutics are designed and identified. Historically, most drugs have been discovered either by isolating the active ingredients from natural sources such as plants, animals, or minerals, or by empirical approaches that capitalized on enlightened serendipity (such as the discovery of penicillin in a dirty petri dish in Alexander Fleming's laboratory, or the invention of aspirin—still the most widely used drug worldwide). Indeed, in developed nations, herbal remedies have become more popular. With rapid advances beginning in the twentieth century in the understanding of the origins and pathology of human disease, modern drug discovery typically focuses on studying the metabolic pathways related to a disease state or pathogen, and manipulating these pathways using medicinal chemistry, biochemistry, physiology, microbiology, and/or molecular biology. Genetic and genomic information also offers great promise in drug discovery and therapeutic success [3].

The first step in the process is *target identification*, and it is this critical step that necessitates a true understanding of the pathogenesis of the disease. Target identification for numerous serious diseases is being pursued aggressively by laboratories in the pharmaceutical industry, universities, and government institutions worldwide. The ideal target is generally a clearly identified molecular entity (such as an enzyme or a receptor) known to be directly associated with the disease pathophysiology. Certain targets are considered to be more likely than others to be amenable to changes that the medicinal chemist can target with compounds that might ultimately lead to a successful medicine. The term *druggability* of a given target (*druggable target*) is being used to indicate the likelihood of being able to modulate a target with a small-molecule drug or antibody, and it is important to predict the potential druggability of a novel target. Parameters that influence druggability include cellular location, specificity, development of resistance, transport mechanisms, side effects, and toxicity. Some target classes, such as protein kinases or the large family of transmembrane receptors such as the G-protein-coupled receptors (GPCRs) have been targeted successfully, and a large number of approved drugs, such as many biogenic amines, eicosanoids, lipid-signaling molecules, and numerous peptide and protein ligands, exhibit their mechanism of action by interfacing with GPCR receptors. The many serious diseases that remain poorly treated may witness breakthroughs due to the exploitation of many unexplored targets.

However, many safe and effective drugs have been and continue to be discovered and developed without a true understanding of the actual target; that is, the mode of action may be known, but the mechanism of action may not be uncovered until later, or not at all. With their longer history, small-molecule drugs currently tend to be focused on the better established targets, while extensive research has been ongoing on new targets for biotherapeutics (i.e., biotechnology-derived drugs such as therapeutic proteins, peptides, oligosaccharides, and monoclonal

antibodies). Also, the concept of “druglike” properties is used by medicinal chemists as a guide to the likelihood of an NCE becoming a successful drug [4]. Such characteristics include physicochemical properties such as lipophilicity, as well as optimal absorption, distribution, metabolism, and excretion (ADME) profiles (Chapter 2), which enable the compound to exhibit targeted efficacy for a sufficient length of time. Indeed, it appears that lipophilicity has emerged as the single best physicochemical characteristic that is predictive of the drug-like property of a chemical regarding potency, efficacy, ADME, and toxicity [4]. This is exemplified by the *Lipinski rule of five* [5,6], which is a rule of thumb describing the molecular properties of a drug that can predict the high absorption and permeability of small-molecule drugs, although the rule does not predict if a compound is pharmacologically active. The rule states that, in general, an orally active drug should not violate more than one of the following four criteria:

1. No more than five hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
2. No more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
3. Molecular weight below 500 Da
4. Calculated octanol–water partition coefficient ($c \log P$) below 5

The Lipinski rule is only applicable for those compounds that are not substrates for active transporters (Chapter 2). An analysis of databases of the past decade of NCE hits and leads have shown that advanced lead compounds and early clinical candidates that have undergone attrition tend to differ in the desirable physicochemical properties described above, and that the undesirable phenomena were traced back to the nature of the high-throughput screening tests and hit-to-lead optimization practices [7]; this reinforces the value of studying druglike properties as early as feasible.

1.2.2 Hit-to-Lead Identification

Following target identification, and for small-molecule chemicals, the medicinal chemist is charged with the responsibility of compound synthesis (e.g., combinatorial chemistry, high-throughput chemistry, classical organic chemistry synthesis, compound libraries) based on numerous strategies and considerations [8]. This is followed by appropriate in vitro [usually by actual or virtual (using computer-generated models) high-throughput screening] and in vivo screens of the new compounds for potential potency and selectivity, and an evaluation of how NCEs with the appropriate characteristics are selected for specific targets of interest. Novel pharmacophores can also emerge by drug design, which involves the prediction of which NCEs might “fit” into an active site based on the biological and physical properties of the target. Thus, these initial evaluations focus on efficacy and potency rather than on potential safety. High-potency drugs are

associated with low-efficacious doses, and in general, the lower the efficacious dose, the less the likelihood of toxicity and side effects.

It is rare that a perfect drug candidate will emerge from these early screens. Typically, several compounds will be uncovered with some degree of activity, and if these compounds share common chemical features, one or more pharmacophores can then be developed. Collaboration between biology and medicinal chemistry is critical such that medicinal chemists can attempt to use structure–activity relationships (SARs) to improve the characteristics of the lead compound(s) [e.g., increase activity against the target selected (potency)], decrease activity against unrelated targets (selectivity), and/or improve druglike properties (e.g., lipophilicity, as described above; metabolic stability). The goal is to improve the properties of the NCEs to allow the most favorable compounds to move forward to later-stage testing (e.g., disease models) in discovery and to enter the early stages of development. This process of drug discovery is discussed in detail in other treatises [e.g., 9,10] and is beyond the scope of this book. A variety of terms are used to define the major consecutive steps of the discovery and early development process following target identification: *hit identification*, *hit confirmation*, *hit to lead*, *lead identification*, *lead characterization*, *lead optimization*, and *bridging from discovery to development*. Realistically, these are not discrete stages of the discovery/early development process but should be viewed as a continuum as an NCE gradually morphs into a candidate drug. These terms are used only rarely in this book; instead, pre-FIH drug discovery implies those activities that occur, starting with lead optimization: that is, those studies that begin to define whether an NCE emerging from discovery is a realistic candidate to enter human trials.

As a general rule, pharmaceutical companies prefer to develop orally active small-molecule drugs, which can be administered conveniently to the patient, ideally once a day. However, many life-threatening diseases have not been attacked successfully by small molecules, and the evolution of biotherapeutics such as therapeutic proteins and peptides, monoclonal antibodies, oligosaccharides, and nucleic acids has revolutionized the industry. These macromolecular drugs pose specific challenges in terms of production, drug delivery, interpretation of animal toxicity studies, and administration to patients (Chapter 12).

1.2.3 Lead Optimization Strategies

To this point we have provided a brief overview of some of the early aspects of the discovery process. As stated, “discovery” and “development” can be considered a continuum; where one ends and the other begins—indeed, whether such a sharp distinction exists—varies among drug sponsors. For purposes of the discussions in subsequent chapters, the development phase is considered to begin when a decision is made to select an NCE for nonclinical development and the initial good laboratory practices (GLP) toxicity studies are planned. The chapters herein describe those discovery support activities, development programs, and support functions, starting when one or more NCEs emerge from *in vitro* and *in vivo*

pharmacological testing as potentially efficacious new candidate drugs through to the recommended plan for the dosage regimen for the FIH trial.

The key challenge in drug development institutions, whether small or large organizations, is to establish a strategy whereby as many of the key properties of NCEs emerging from pharmacological testing as possible are evaluated in the most efficient and effective manner. There is, of course, no ideal drug, but some of the characteristics that can be considered important in the decision as to which of several compounds will be selected for pre-FIH development are listed in Table 1.1. This list should not be considered a boiler plate compendium, as the common thread throughout the pharmaceutical industry is that no two

TABLE 1.1 Some Optimal Characteristics Evaluated During the Discovery Phase for Orally Administered Drugs

Drug Property	Characteristic	Purpose
Potency	High target affinity	Lowest efficacious dose is desirable
Selectivity	Low affinity for related targets	Minimize side effects associated with other targets
Biology	Significant activity in a cellular assay	Demonstration of activity in a whole cell system
Chemical stability	Should be chemically stable	Pharmaceutical and bioavailability goals
Chirality	Should be a single stereoisomer if the NCE has a chiral center	Racemates should not be developed
Patent status	Free of intellectual property	Hit compound structures must be patentable
Physicochemistry	Appropriate lipophilicity	Desire druglike properties
Metabolism	High metabolic stability in vitro	Can predict relative clearance and dose frequency
Enzymology	Not a potent enzyme inhibitor or inducer	Can predict potential clinical drug–drug interactions
Bioavailability and pharmacokinetics	Oral bioavailability should be sufficiently high and dose related	Activity requires systemic exposure
Permeability	Exhibits cell membrane permeability	Drug must be absorbed and reach target
Drug transport	Not a potent inhibitor of P-glycoprotein	Transporters are barriers to drug uptake and distribution
Toxicity	Not cytotoxic (exception: some anticancer drugs) or mutagenic	Early signal of unwarranted toxicity
Safety pharmacology	Cardiac hERG channels	Major undesirable side effect for most drugs

companies would have identical strategies as to what should be included in, or excluded from, this list. For example, protein binding has not been included, as it is not considered by this author to be a key variable in the early decision-making process, although other investigators may view its importance as greater in the discovery paradigm. However, most drug sponsors would want to assure that most of these key properties have been studied prior to recommendation for pre-FIH development. In the chapters that follow, the assumption is made that the first seven properties—potency, selectivity, biology, chemical stability, chirality, patent status, and physicochemistry—have been studied appropriately such that the emerging NCEs can proceed through the gate for evaluation. Discussions are presented on the lead optimization and pre-FIH development programs principally for orally administered small-molecule drugs and systemically administered biotherapeutics, along with the regulatory expectations and various planning strategies for the critically important FIH trial.

1.3 PRE-FIH DRUG DEVELOPMENT

1.3.1 Introduction

Drug development refers to the activities undertaken after an NCE has been identified as a potential drug candidate to evaluate its suitability as a medication. In the context of this book, NCEs are considered to be compounds that emerge from the drug discovery process based on promising activity against a biological target(s) thought to be important in the target disease, and have been selected for GLP toxicity trials based on optimal lipophilicity, in vitro metabolism, nonclinical pharmacokinetics/bioavailability, and possibly preliminary safety pharmacology and/or in vitro toxicity tests. In the next few sections of this chapter we present some general perspectives of pre-FIH development and the FIH trial, most of which are covered in detail in subsequent chapters.

1.3.2 Pre-FIH Toxicology

Once an NCE has been selected as a feasible drug candidate, in vitro and in vivo studies are initiated to evaluate the drug's toxicity (Chapter 7). Acute toxicity involves harmful effects in an organism through a single or short-term administration, although its utility in the overall toxicology program may be waning. Chronic toxicity is the ability of a drug candidate to cause untoward effects after multiple administrations over an extended period of time. The goals are to identify organs targeted by the drug, effects on mammalian reproduction, and for drugs to be administered chronically, whether there are any long-term carcinogenic effects. These nonclinical safety evaluations are conducted according to strict regulatory procedures called *good laboratory practices* (GLPs) (Chapter 9). Toxicity evaluations are among the first development studies to be conducted on a candidate drug, and will continue concurrently through the course of the clinical development phases. The interpretation of toxicity findings is often different

for small-molecule drugs than for biopharmaceutics; for some biologics, there are issues with “superpharmacology,” wherein there is too much of a desired response being responsible for the adverse effects observed.

During the pre-FIH phase, the *in vivo* studies typically conducted are limited to a 2-week to 3-month duration (depending on the duration of use in humans) in a rodent and nonrodent species, whose choice is based on which is believed most closely correlated to humans. Species differences in gastrointestinal tract physiology, intrinsic enzyme activities, circulatory system, bioavailability, or metabolic profiles will render some species more appropriate than others. Also, certain classes of drugs may not be relevant in some species; for example, rodents are poor models for antibiotic drugs because the resulting alteration to their intestinal flora can cause significant adverse events that are not relevant for humans. Some species are used for similarity to specific human organ systems (e.g., swine for dermatological products, dogs for gastric studies). Species selection for pre-FIH toxicity studies should be made very carefully in light of the delays and additional expense that might occur (e.g., for new dose-ranging studies; see Chapter 7) should it be considered advisable to change the species at later stages of development.

The promising young field of toxicogenomics is emerging as a possible alternative to animal toxicology testing. These cell-based assays offer a compelling strategy for the evaluation of specific potential toxicity (e.g., the effect on gene expression in hepatocytes) with the hope that this discipline can be employed to reduce the use of whole animals. The dilemma is whether such *in vitro* models or toxicity biomarkers can be roughly equivalent to the classically used *in vivo* models and whether cell-based screens can ever replace animal testing. Perhaps toxicogenomics may best be employed at the early screening stages as a predictive toxicology tool to eliminate NCEs in the discovery phase. There is a critical need to develop and “validate” toxicogenomic high-throughput assays and other models which can at least partially replace current resource-intensive animal testing. Of course, all whole-animal models themselves have shortcomings in predicting human safety, although some modified animals, such as genetic knock-outs, knock-ins, or transgenic models, can be used for specific purposes. In the meantime, it appears that the classical testing of a rodent and a nonrodent species for toxicity properties will remain the gold standard for the foreseeable future.

1.3.3 Formulation and Drug Delivery

The formulation and delivery of drugs into the human body forms an integral part of the drug discovery and development process (Chapter 5). Indeed, formulation issues can influence the design of the lead molecules and feed back into the iterative lead optimization cycle as well as nonclinical and clinical evaluations. The goals of formulating drug substances into drug products is to assure optimal stability and absorption for oral products (e.g., by enhancing absorption through their interaction with the cell membrane of the gastrointestinal tract) and solubility for systemically administered drugs. Indeed, a significant number of drug

discovery and development programs center around new ways of formulating known or marketed drugs in order to improve on their pharmacokinetic profiles, thereby enhancing their safety and/or efficacy characteristics, or improving on the dose regimen (dose level or dose frequency). Components of formulation substances that are not generally regarded as safe (GRAS) become part of the nonclinical safety assessment program (i.e., they must be “qualified”). Sometimes side effects such as local irritation or allergic reactions are attributable to drug formulation rather than the active pharmaceutical ingredient (API).

One of the key logistical challenges in the initiation of pre-FIH toxicity studies is the timely availability of drug substance (or drug product, if formulation is required). It is not uncommon, upon deciding that a lead candidate is to become a candidate drug to undergo toxicity testing, for a drug sponsor to experience the frustration of delays in the synthesis and testing of sufficient amounts of drug required for the animal studies. In most instances, the synthetic route used to generate milligram (or low-gram) quantities of the drug in support of discovery and early development is not feasible for scale-up to the high-gram or possibly kilogram amounts needed for rodent and nonrodent toxicity evaluations. Accessibility of cost-effective starting material can become an issue. There is a “catch-22” element to such delays, in that resources should not be devoted to scale-up synthesis of compounds which may not become candidate drugs, yet once a decision is made to proceed to humans, it is desirable to schedule the toxicity studies as rapidly as possible with sufficient amounts of high-quality drug. It is thus important that representatives of the various disciplines that comprise the project team (Chapter 13) work closely together so as to minimize such inherent delays in the early development process.

1.3.4 Pre-FIH Drug Metabolism and Pharmacokinetics

As with the other major disciplines that comprise the nonclinical and clinical evaluations of candidate drugs [toxicity testing; CMC (chemistry, manufacturing, and controls)], evaluation of the ADME and pharmacokinetic properties of a drug candidate (Chapter 2) is a continuum beginning with support of discovery through to the NDA. This also applies to bioanalytical support of the discovery and development programs (Chapter 4) and the toxicokinetic evaluations (Chapter 8) required to demonstrate that there is a correlation between dose regimen in the toxicity studies with systemic exposure to relevant drug-derived material [parent drug and/or metabolite(s)].

As stated previously, the reason that pharmacokinetic (PK) and ADME characteristics are no longer the principal cause of attrition during drug development or of drug withdrawals postmarketing due to untoward drug–drug interactions (e.g., withdrawals of Posicor in 1998 or Hismanal in 1999) is that technologies are now being utilized during the discovery phase to weed out those NCEs that have poor such characteristics. Within the armamentarium of available rapid ADME, bioavailability, and bioanalytical testing procedures and laboratory equipment, the discovery unit must decide what to do when and with what; that is, medicinal

chemists can rapidly generate numerous compounds which, with high-throughput techniques, can rapidly be evaluated for biological activity. Thus, discovery support ADME groups can become flooded with numerous NCEs and be asked to “tell us which compounds have good ADME/PK properties.”

Strategic planning is critical in determining which studies should be done early and which can be deferred until later. Certainly, it is desirable to have an early assessment in vitro in human preparations of metabolic stability and cytochrome P450-mediated enzyme inhibition, as well as some indication of oral bioavailability in laboratory animals (pharmacology and/or putative toxicity species) (Table 1.1). Other possible discovery support tests are decided on a case-by-case basis; for example, although it is necessary to evaluate plasma protein binding of a drug undergoing clinical development, it is probably not necessary to have this information as part of the go/no go decision package during discovery or during pre-FIH development. Permeability and transporter assays are readily available to characterize drug uptake into, or efflux from, the target organ(s), and depending on the emerging properties of the NCEs being examined, the project team will decide if this assay is also relevant in compound selection. As most drugs undergo at least some biotransformation, a strategy is recommended regarding how much metabolism work should be conducted at this stage, as metabolites may also contribute to pharmacological activity, or with in vitro tests that do not involve metabolic activation [e.g., cardiac hERG (human ether-a-go-go related gene) channel assay; Table 1.1], a negative finding is valid for a parent drug but not for putative metabolite(s).

Once the decision is made to proceed to conduct pre-FIH toxicity studies, it is necessary to develop and fully validate the bioanalytical assay for the drug in plasma of the animal species selected (Chapter 4), to analyze the plasma samples, and to perform the toxicokinetic analyses to assess systemic exposure (Chapter 8). During this stage it is also advisable to time the validation of the bioanalytical assay for human plasma such that there will be no delay in such analyses once the FIH trial is initiated. The only regulatory ADME/PK requirements or expectations for ADME/PK in IND submissions are typically comparative in vitro data on metabolism across species (toxicity species and humans) and toxicokinetic support of the pre-FIH toxicity trials. Often, however, it is in the interest of the sponsor and for investigational review boards to have additional information that can help support predictions of safety and efficacy in initial human studies.

1.4 THE FIH TRIAL

The first administration of a drug candidate to human subjects is arguably the most exciting moment on the development path and the time that probably generates the highest anxiety, for this study represents the culmination of all the pre-FIH activities and results in the generation of initial data on the safety and possibly pharmacokinetics of the candidate drug in the target species. Up to this point, all of the information available has been based on in vitro and nonclinical

pharmacology, toxicology, and ADME models, some of which may or may not be reliable indicators of human response. Also, this stage often involves change from a nonclinical champion of the NCE to a clinical champion on the development team.

It is critical that the FIH trial be designed appropriately so as to address its primary purpose: that is, to characterize the safety, tolerability, and pharmacokinetics of the NCE, including an evaluation of its maximum tolerated dose. Efficacy is rarely a primary goal of the FIH trial, as they are generally insufficiently powered to assess a relevant pharmacodynamic endpoint and the studies are typically conducted in healthy volunteers rather than in patients. However, it could be extremely useful if some biomarker of pharmacodynamic activity were available to be included in the FIH trial.

There are several challenges in the design and implementation of an FIH trial. The primary challenge is selection of the starting dose, the dose escalation strategy, and the stopping dose (Chapter 10), based generally on the totality of safety and plasma exposure data emerging from the pre-FIH toxicity studies (Chapter 7) as well as the results from the safety pharmacology studies (Chapter 6). The second challenge is to assure that all resources are available in a timely manner (e.g., sufficient appropriately tested drug product and fully validated bioanalytical assay). Thus, it is important that representatives from all the various disciplines involved in generating the relevant data—nonclinical pharmacology, toxicology, safety pharmacology, drug metabolism and pharmacokinetics, formulation development—contribute to the important decision regarding the starting dose and study design of the FIH trial.

1.5 THE REGULATORY LANDSCAPE

Drug development is different from other high-tech ventures in that it is highly regulated, although some outside the industry would argue that it is not regulated enough. There is no doubt that the tough new regulatory landscape is altering drug development strategies. It is important that the pharmaceutical industry appreciate that regulatory authorities in the United States [11], Europe [12], and elsewhere have become more demanding regarding the adequacy of benefit/risk assessments, particularly in the wake of high-profile withdrawals by the FDA of drugs such as Vioxx. Industry commentators have suggested that the increased risk aversion by regulatory agencies, resulting in larger clinical trials, is a contributor to the recent decreases in new drug approvals. On the other hand, regulatory authorities tend to argue that fewer drugs are being approved because pharma has filed fewer NDAs, due to faltering research efforts. More clarity is being sought by drug sponsors as to the regulatory tolerance for risk, which hopefully will not be a moving target given the myriad medical, scientific, political, and business interests that are interacting with government officials. Also, uncertainty exists as to how the some 200 new provisions in the FDA Amendments Act of 2007 will affect agency requirements. Although some drugs still reach the market without

adequate assessment of efficacy, it is important to note that marketed drugs are rarely withdrawn due to poor quality or efficacy, and that the percentage of marketed actually drugs withdrawn due to patient risk is quite low. The latter include:

- 2007: aprotinin (Trasylol)—increased complications or death
- 2007: tegaserod (Xelnorm)—heart attack and stroke
- 2007: pergolide (Permax)—risk of heart valve damage; still available outside the United States.
- 2006: ximelagatran (Exantia)—increased hepatotoxicity
- 2005: pemoline (Cylert)—increased hepatotoxicity
- 2004: rofecoxib (Vioxx)—risk of myocardial infarction (the most publicized withdrawal in recent years)

Although marketing of approved therapeutics is generally targeted worldwide, our heterogeneous world results in regional differences, such as varying standards of care, population dynamics such as ethnic and metabolic features, and emerging markets (Asia-Pacific; Latin America; Eastern Europe; Middle East/Africa) with different regulatory challenges and opportunities (Chapters 14 and 15). Historically, three main regulatory bodies have dominated the global oversight of drug approvals:

1. The U.S. Food and Drug Administration (FDA)
2. The European Medicines Agency (EMA)
3. The Japanese Ministry of Health, Labor, and Welfare (MHLW)

A gigantic step in attempts to globalize and harmonize regulatory guidelines was the establishment in 1992 of the International Conference of Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), which brought together representatives from the FDA, EMA, and MHLW, together with their industry counterparts from the U.S. Pharmaceutical Research and Manufacturers Association (PhRMA), the European Committee for Proprietary Medicinal Products (EC-CPMP/EFPIA), and the Japanese Pharmaceutical Manufacturers Association. Representatives from other countries, including Canada (Health Canada) and Australia (Therapeutic Goods Administration), also participated. The goal was to attempt to develop an international consensus on the scientific, technical, and regulatory aspects of drug development and product registration, and to make the regulatory processes more transparent with the generation of “harmonized” guidelines that would be applicable worldwide (www.fda.gov/cber/ich/ichguid.htm). These common requirements agreed upon by the major regulatory bodies have simplified at least some of the drug development processes, have reduced duplication due to regional regulatory differences, although regional guideline documents that remain still take precedent within the respective geographical areas. Regarding IND submissions, one of the

major benefits that emerged from ICH is the ability to submit INDs electronically worldwide using the common technical document format (eCTD). The ICH process is a growing initiative which continues today, and the FDA, EMEA, and MHLW continue to harmonize their policies on a broad range of regulatory issues, much of which is discussed in later chapters.

In addition to the sections that describe the common technical document (CTD) (with prefix letter “M”) format for submission of marketing applications to regulatory agencies (Chapter 15), the ICH guidance documents, some of which are relevant to pre-FIH development studies, are divided into three general categories:

1. *Safety*. These guidances, designated with the prefix letter “S,” refer to non-clinical safety, but not clinical safety, and describe the short- and long-term toxicity studies for small-molecule drugs and biopharmaceutics. Included are genotoxicity tests, reproductive toxicology, immunotoxicity evaluations, and carcinogenicity studies. Also included in this category are support functions such as toxicokinetics, safety pharmacology (including QT-interval prolongation), and tissue distribution studies.

2. *Quality*. These documents, designated with the prefix letter “Q,” fall under the general category of chemistry, manufacturing, and controls (CMC) for small-molecule drugs and biopharmaceutics. Included are stability testing procedures, validation of analytical methodologies for drug substance and impurities, dissolution testing, good manufacturing practices (GMPs), and other relevant guidances.

3. *Efficacy*. These documents, designated with the prefix letter “E,” describe various aspects of efficacy as well as safety evaluations conducted in human subjects. Included are good clinical practices (GCPs), dose–response approaches, special populations (e.g., pediatrics and geriatrics), statistical principles, data management, structure and content of clinical study reports, acceptability of foreign clinical data, and other clinical support documents.

Regulatory authorities continue to issue guidances or guidelines independent of ICH. It should be noted that although a *regulation* is legally binding (such as GLP regulations, Chapter 9; GMPs; GCPs), *guidances* are technically just a recommendation and are nonbinding. As stated in the preamble to the FDA guidance Web page (www.fda.gov/CDER/GUIDANCE), “Guidance documents represent the agency’s current thinking on a particular subject.” However, it is wise for sponsors to consider the contents of regulatory guidances as expectations, and any planned deviations should be subject for discussions with the FDA or other relevant agencies (Chapter 14).

1.6 CONTRACT RESEARCH ORGANIZATIONS

One of the most valuable resources available for sponsors to support discovery and development programs is the wide variety of institutions known as contract research organizations (CROs). The use of such organizations is mentioned

in passing in several chapters of this book. The term *CRO* originally referred to “clinical research organization,” as initially, in the early 1980s, such discrete institutions were involved solely in phase III clinical trials. At that time, various government entities were outsourcing clinical testing under grants and contracts. Throughout the past three decades, CRO functions have expanded to encompass a wide array of discovery and development functions (Table 1.2), to include both nonclinical and clinical activities, and to support functions such as CMC (for contract formulation and testing) and analytical/bioanalytical assay

TABLE 1.2 Some Contract Research Organization Functions and Activities

Stage of R&D	Function	Activity
Drug discovery	Basic research	Target identification and validation
		Hit-to-lead optimization
		Lead optimization
	Chemistry	Medicinal chemistry
		Custom synthesis
	In vitro studies	Target enzyme kinetics
		Receptor binding
		ADME screens (e.g., metabolic stability, enzyme inhibition)
	Bioanalytical	Toxicity screens (e.g., Ames test)
		Partially validated assay (non-GLP)
In vivo studies	Efficacy evaluation	
	Preliminary bioavailability	
Nonclinical development	CMC	Drug substance synthesis
		Preformulation design
		Formulation development
		Specification analyses (e.g., stability, impurities)
		Analytical services
	Toxicology	Pre-FIH safety in rodent and nonrodent (GLP)
	Bioanalytical	Validated assays for toxicology species (GLP)
	ADME/PK	Toxicokinetics and additional ADME
Safety pharmacology		
Clinical development	CMC	Manufacture of GMP drug product
		Other activities similar to nonclinical
	Clinical trials	Trial design and protocol preparation
		Trial conduct and management
		Central laboratory services
		Medical writing
	Bioanalytical	Validated assay(s) for human matrices
Support services	Quality assurance	Both nonclinical and clinical development
	Regulatory	Data management (nonclinical and clinical)
		IND preparation and filing
		NDA preparation and filing

development, validation, and sample analyses. The advent of liquid chromatography-mass spectrometry (LC-MS/MS) as a sensitive and specific bioanalytical tool led to an explosion of new specialty CROs in the early 1990s. Today it is possible to outsource virtually all components of drug discovery and development. The role of the CRO is to provide complementary capabilities for a sponsor company's in-house operations. At the other end of the scale, the range of expertise of CROs can enable "virtual" companies to develop and register drug candidates with no internal resources with the exception of management personnel in collaboration with outside scientific, clinical, and regulatory consultants.

The availability of CROs enables drug research and development institutions to develop strategies that combine internal and external resources in the most efficient possible manner. This is certainly the case when considering the use of nonclinical CROs that specialize in discovery support and nonclinical development. In the ideal world, drug sponsors would conduct all studies in-house; in this manner, resources (time/staff/cost) and flexibility are under the direct control of the sponsor company. However, even big pharma companies find the need to utilize the services of CROs for those studies for which expertise is not available internally, or it is deemed more efficient to outsource. Indeed, given the growing number of available services and the attraction for high-quality scientists to become part of the CRO industry, it is often advisable to outsource to CROs even though studies could be set up and performed in-house. Such considerations are company specific.

CROs come in all shapes and sizes: from the multinational "one-stop shopping" (or so they say) organizations to smaller specialty laboratories, some of which are associated with academic institutions; there are currently some 500 CROs worldwide competing for business [13]. When a sponsor firm decides to outsource to a nonclinical CRO or contract formulator for their pre-FIH programs, many considerations must be taken into account. Although too numerous to include, some of those considerations, many of which also apply to clinical CROs, include the following:

1. *Choose the CRO carefully.* There is nothing more wasteful in the drug discovery and development business than to conduct poor quality studies which generate equivocal answers (i.e., garbage in—garbage out). This will often occur if a sponsor uses cost as the primary variable in CRO selection. Although it is important to generate competitive bids for study conduct from two or more CROs, those companies selected to submit bids should be high-quality organizations with an established positive reputation. CRO providers can be located by attending relevant scientific meetings. Sponsors should make independent inquiries about the CRO and/or to arrange for qualified personnel to visit the CRO site for a due-diligence evaluation. Some key criteria for CRO selection include, but are not limited to, the following:

- Quality of the scientific staff (especially the study director) and equipment
- Problem-solving abilities and data interpretation capabilities

- Company and staff stability (e.g., whether economics has resulted in recent staff reductions or changes that may affect their operations)
- Experience in specific study and/or therapeutic area
- Operational efficiency and flexibility
- Relations with regulatory agencies (including results of recent FDA inspections and severity of FD-483 citations, which should be requested for review)
- Record keeping (including sample-handling procedures) and documentation [including standard operating procedures (SOPs)]
- Management oversight of operations
- Quality and efficiency of quality assurance oversight of operations and review of data (if applicable)
- Quality of written documentation

If overall quality, experience, and level of service are deemed to be similar, cost and other variables, such as turnaround time, should affect the selection. When bids are received, the sponsor should assure that they understand the rationale for the cost of each line item and should request more detailed breakdown should such clarity not be readily apparent. Although this may appear to be obvious, it is important to assure that bid comparisons are made based on identical study designs and deliverables and that no hidden costs will emerge after study initiation. It should also be noted that with the globalization of larger CROs, the due-diligence results from one site may not apply to newer sites of the same company, such as in Eastern Europe, India, China, or Latin American; if outsourcing to such sites is considered because of potential cost savings, they should be treated as discrete companies which should be subject to a separate due-diligence evaluation.

2. *Review the sponsor/CRO culture.* It is important that the drug sponsor view the putative CRO as an extension of their own institution. The relationship between the two organizations must develop into a business partnership, and thus it is critical that smooth communication be established between the sponsor and the CRO. A sponsor project manager or management team (see also consideration 4 below) should be responsible for the supervision of the CRO and would interface with one or more point persons from the CRO. Such interactions should occur on several relevant occasions during performance of the study. Once a relationship has been established with initial studies, subsequent studies should run more smoothly. It should be noted that the CRO should not be asked to provide overall program leadership; this must remain the responsibility of the sponsor. Project management within the sponsor company will act in its best interests: for example, to determine whether multiple providers with specific specialists are advisable, or whether a single large CRO with multifaceted capabilities works to the sponsor's advantage.

3. *Prepare with great care.* The sponsor must recognize that CROs are for-profit businesses and that there is nothing more wasteful, stressful, or frustrating

for a CRO than dealing with an unprepared client. “High-maintenance” sponsors may be charged more for the same study than a client known to be well prepared [14]. Preparation involves proper planning by the client company regarding study goals and anticipated deliverables, including agreement on report format. Small pharma/biotech or virtual companies with minimal internal scientific expertise should not only rely on advice from CROs but should utilize an independent consultant working on behalf of the client. Proper preparation also involves assurance that the drug substance or drug product is available to the CRO on time; lack of drug availability is the principal cause for study delay and may result in increased cost due to disruption of the CRO schedule. The sponsor should also provide other appropriate information to the CRO, such as any documentation or reports (e.g., certificate of analysis, bioanalytical report for toxicokinetics) for inclusion in the final report.

4. *Monitor the studies.* With the possible exception of small or specialty studies for which the CRO has a reputation for excellence (e.g., receptor binding, in vitro metabolism; enzyme inhibition, Ames test), it is in the sponsor’s interest to monitor critical aspects of the study with a well-trained sponsor representative who will be charged with auditing the conduct of the study for, where relevant, protocol, SOP, and GLP compliance as well as critical components such as the first day of animal dosing for toxicity or ADME/bioavailability studies and necropsy for toxicity studies. Reputable CROs are usually very comfortable with such a monitor, as they welcome the independent eyes of the external representative. Study monitoring also helps to solidify the partnership that should develop between the CRO and the drug sponsor.

5. *Review all documentation carefully.* It is important to critically review the contract with the CRO, and for the sponsor to understand the fee structure and the CRO’s policies on study changes, delays, cancellation fees, and so on. The second document that requires very close scrutiny is the study protocol, and it is important that the sponsor spend sufficient time with the CRO regarding protocol preparation and careful review to assure that it satisfies the study goal(s) (which should be clearly stated). As all studies are protocol driven, this document determines the subsequent path moving forward. Finally, draft and final reports require careful review by experts of the various disciplines that comprise the study conduct.

1.7 CONCLUDING REMARKS ON INTRODUCTORY PERSPECTIVES

The interval from lead optimization through to initiation of the FIH trial represents the first opportunity to evaluate the potential of the NCE, selected on the basis of its initial positive pharmacological properties, to become a successful therapeutic. Those involved at this pre-FIH stage, as well as the clinical phases of drug development, are subject to numerous forces, not the least of which is the pressure for corporate profit and therefore the tendency to try to force the NCE

to possess optimal safety and efficacy. This becomes a balancing act, because independent of such factors as resources (time/cost/staff), internal champions, corporate strategies, and portfolio management goals, the NCE must be viewed as the boss of the exercise. This is very tricky, since there is no such thing as a perfectly efficacious and safe drug. Also, an NDA that has been submitted may be approvable, but will the resulting marketed drug really be a valuable addition to the therapeutic armamentarium and thereby generate sufficient profits for the drug sponsor? All studies must be designed carefully and the results interpreted dispassionately such that appropriate decisions can be made as to whether development should continue. One of the most difficult tasks within any size of a drug development organization is to make the difficult decision to terminate development of what had seemed to that stage to be a promising candidate drug. However, there is nothing more wasteful than to continue to push for a drug candidate to elicit therapeutic properties that it does not possess. It is thus incumbent upon all disciplines, certainly at the pre-FIH stage when several go/no-go decisions should be in place, to work together and determine unemotionally the true risk/benefit potential for the specific target disease and patient population.

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