Drug Safety Evaluation

Third Edition

Shayne Cox Gad

WILEY

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To the memory of my mother Norma Jean Cox Gad, who crossed over nine years ago, and my brother Scott Michael Gad who joined her six years ago. I hope that all your beloved little friends are there with you. I will see you both again.

—Shayne Cox Gad

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While all of my interns assisted in the preparation of this volume, its completion would not have occurred without the efforts of Leslie Eagle and indexing by my beloved wife, Novie Beth Ragan Gad.

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PREFACE

The third edition of *Drug Safety Evaluation* is a complete revision of the second edition which maintains the central objective of presenting an all-inclusive practical guide for those who are responsible for ensuring the safety of drugs and biologics to patients and shepherding valuable candidates to market, healthcare providers, those involved in the manufacture of medicinal products, and all those who need to understand how the safety of these products is evaluated. The many changes in regulatory requirements, pharmaceutical development, and technology have required both extensive revision to every chapter and the addition of four new chapters.

This practical guide presents a road map for safety assessment as an integral part of the development of new drugs and therapeutics. Individual chapters also address specific approaches to evaluation hazards, including problems that are encountered and their solutions. Also covered are the scientific and philosophical bases for evaluation of specific concerns (e.g., carcinogenicity, development toxicity, etc.) to provide both understanding and guidance for approaching new problems. *Drug Safety Evaluation* is aimed specifically at the pharmaceutical and biotechnology industries. It not only addresses the general cases for safety evaluation of small and large molecules but also all of the significant major subcases: imaging agents, dermal and inhalation route drugs, vaccines, and gene therapy products. It is hoped that the approaches and methodologies presented here will show a utilitarian yet scientifically valid path to the everyday challenges of safety evaluation and the problem solving that is required in drug discovery and development.

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Shayne Cox Gad, B.S. (Whittier College, Chemistry and Biology, 1971) and Ph.D. in Pharmacology/Toxicology (Texas, 1977) DABT, ATS, is the principal of Gad Consulting Services, a 24-year-old consulting firm with seven employees and more than 450 clients (including 200 pharmaceutical companies in the United States and 50 overseas). Prior to this, he served in director-level and above positions at Searle, Synergen, and Becton Dickinson. He has published 48 books and more than 350 chapters, articles, and abstracts in the fields of toxicology, statistics, pharmacology, drug development, and safety assessment. He has more than 39 years of broad-based experience in toxicology, drug and device development, statistics, and risk assessment. He has specific expertise in neurotoxicology, *in vitro* methods, cardiovascular toxicology, inhalation toxicology, immunotoxicology, and genotoxicology. Past president of the American College of Toxicology, the Roundtable of Toxicology Consultants, and three of SOT's specialty sections. He has direct involvement in the preparation of INDs (110 successfully to date), NDA, PLA, ANDA, 501(k), IDE, CTD, clinical databases for phase 1 and 2 studies, and PMAs. He has consulted for FDA, EPA, and NIH and has trained reviewers and been an expert witness for FDA. He has also conducted the triennial toxicology salary survey as a service to the profession for the last 27 years.

Dr. Shayne Cox Gad is also a retired Navy line officer.

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THE DRUG DEVELOPMENT PROCESS AND THE GLOBAL PHARMACEUTICAL MARKETPLACE

1.1 INTRODUCTION

Pharmaceuticals are a global industry, grossing $839 billion (US dollars) in 2014. They are developed to benefit (and sell to) individuals and societies worldwide. Their effectiveness and costs affect, directly or indirectly, all of us.

This third edition focuses (as its predecessors did) on the assessment of the safety of new drugs. In the broadest sense, this means it must address not only the traditional "small molecules" that have dominated the field for the last century and the large therapeutic molecules derived from biotechnology sources but also vaccines, biologics such as blood and blood products, cell therapies, and excipients. The globalization of the regulation of the safety, efficacy, and manufacture of pharmaceutical products comes from the success of the International Conference on Harmonisation (ICH) process. But, as will be seen, the same globalization of the industry and continuous advances of science have also led to market diversification of the types and use of drugs, and with this, regulatory drug safety evaluation requirements continue to fragment, which has made things more complex rather than simpler (Alder and Zbinden, 1988; Gad, 2011).

1.2 THE MARKETPLACE

The world marketplace for drugs is large, although the majority of sales are in the three regions: in 2013 about 39% of the pharmaceutical market resided in the United States, 24% in Europe, 15% in Japan, and 22% in emerging markets. The balance of sales is spread across the globe. This does not mean, however, that marketing applicants can or should ignore the requirements of other countries, for example, Indonesia. Approval processes in these countries can, at times, be as rigorous as in any other regulatory authority domain.

Pharmaceuticals in all their forms compete today as part of a global market, though one which serves (and is available to) different parts of the world's population to varying extents.

The term "pharmaceuticals" is here used in the broadest sense of man-made therapeutics: small molecules, large protein moieties, vaccines, blood products, and, as must be, their attendant components (excipients, impurities, and all) to different degrees and in different types of products.

According to the IMS 2013 global pharmaceutical market and therapy forecast, the global market for regulated drugs (as differentiated from dietary supplements, herbal products, and nutraceuticals) is estimated to be some $870 billion in 2014 (US dollars). In 2015, there were 109 individual products with annual sales in excess of $1 billion (i.e., "blockbusters") which have tended to be the focus of pharmaceutical development until recently and the impending demise of patents on which is changing the industry (Table 1.1).

This concentration of total sales in a limited number of products (e.g., there are currently more than 22 000 approved prescription drugs in the United States) is widely held to have distorted the therapeutic aspects of new drug development but is now starting to undergo change (back to) a paradigm that looks at a decreased emphasis on the billion dollar "blockbuster" drugs.

Widely misunderstood is the extent and diversity of the pharmaceutical R&D sector. While precise numbers are unavailable (and meaningless, as companies are continuously being started, merged, or going out of business, though the overall trend is to increased numbers), best estimates place the

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TABLE 1.1 Top 20 Selling Pharmaceuticals (2013)

Rank	Drug	Current Manufacturer	Total Sales (USD)	% Change from 2012	Primary Disease/Medical Use	Route(s)
1	Abilify	Otsuka Pharmaceutical Co. Ltd	6 293 801	+11	Psychotic conditions, major depressive disorder	Oral, injection
2	Nexium	Astra Zeneca Pharmaceuticals, LP	5 974 550	+5.4	GERD, Zollinger-Ellison syndrome, erosive esophagitis, other conditions associated with excessive stomach acid	Oral, parenteral
3	Humira	AbbVie, Inc.	5 428 479	+20.75	Inflammation (arthritis, ankylosing spondylitis, plaque psoriasis, and hidradenitis suppurativa, Crohn's disease or ulcerative colitis after other methods fail)	Injection
4	Crestor	Astra Zeneca Pharmaceuticals, LP	5 195 930	+8.3	Cholesterol	Oral
5	Cymbalta	Eli Lilly and Company	5 083 111	+12	Depression, Anxiety	Oral
6	Advair Diskus	GlaxoSmithKline	4 981 108	+7.3	Asthma	Inhalation
7	Enbrel	Amogen, Inc.	4 585 701	+12.9	Arthritis, or ankylosing spondylitis, plaque psoriasis and polyarticular juvenile idiopathic arthritis	Injection
8	Remicade	Centocor Ortho Biotech, Inc.	3 980 556	+6.5	Arthritis, ulcerative colitis, Crohn's disease, ankylosing spondylitis, plaque psoriasis	IV
9	Copaxone	Teva Pharmaceuticals	3 603 958	+7.5	Multiple Sclerosis	Injection
10	Neulasta	Amogen, Inc.	3 472 969	+4.1	Neutropenia caused by receiving chemotherapy	Injection
11	Rituxan	Genetech, Inc. (member of Roche group)	3 208 525	+2.5	Non-Hodgkin's lymphoma or chronic lymphocytic leukemia	IV
12	Spiriva	Boehringer Ingelheim Pharmaceuticals, Inc	2 943 778	+8.5	COPD, bronchitis, emphysema, asthma	Inhalation
13	Lantus Solostar	Sanofi (formerly Sanofi Aventis)	2 926 949	+29.5	Diabetes	Injection
14	Atripla	Gilead Sciences, Inc.	2 794 285	+2.5	HIV	Oral
15	Januvia	Merck & Co., Inc.	2 770 995	+9.8	Type 2 Diabetes	Oral
16	Avastin	Genetech, Inc. (member of Roche group)	2 617 373	+2	Brain tumor, certain types of cancers of the kidney, lung, colon, rectum, cervix, ovary, or fallopian tube. Cancer of the membrane lining the internal organs in the abdomen	IV
17	Lantus	Sanofi (formerly Sanofi Aventis)	2 505 281	+12	Type 1 or type 2 diabetes	Injection
18	OxyContin	Purdue Pharma LP	2 462 851	−8.6	Moderate to severe extended pain	Oral
19	Lyrica	Pfizer Inc.	2 357 959	+18.4	Control of seizures, fibromyalgia, diabetic neuropathy, herpes zoster, post-herpetic neuralgia, or neuropathic pain associated with spinal cord injury.	Oral
20	Epogen	Amogen, Inc.	2 206 624	+5.5	Anemia in patients with chronic kidney disease, HIV patients, and cancer patients receiving chemotherapy	Injection. IV

Drugs.com (2014).

TABLE 1.2 Top 25 Drug Companies by sales (2014)

Company	Pharma sales 2014 ($ million)	% Change from 2013
Novartis	47101	–1
Pfizer	45708	–5
Roche	39120	0
Sanofi	36437	–2
Merck & Co.	36042	–4
Johnson & Johnson	32313	15
GlaxoSmithKline	29580	–11
AstraZeneca	26095	1
Gilead Sciences	24474	127
Takeda	20446	7
AbbVie	20207	8
Amgen	19327	6
Teva	18374	0
Lilly	17266	–18
Bristol-Myers Squibb	15879	–3
Bayer	15486	4
Novo Nordisk	15329	3
Astellas	14099	4
Boehringer Ingelheim	13830	–12
Actavis	13062	51
Otsuke	11308	1
Daiichi Sankyo	10430	–14
Biogen Idec	9398	41
Baxter	8831	6
Merck KGaA	7678	–9

PMLive (2015).

number of companies directly involved in discovering and developing new drugs in the United States and Canada at about 3800, 10% of which are publicly traded. There are an equal number in Europe and significant numbers in many other parts of the world (Japan, China, Australia, India, and Israel, to name just a few other countries). While most of the public focuses on very large companies, such as those in Table 1.2, there are many more midsize and small companies.

Starting in 1984 with the Drug Price Competition and Patent Term Restoration Act (better known as the Hatch–Waxman Act), "doses" of small molecule drugs leaving the period of patent protection could be introduced into the marketplace by an ANDA-approved route—a much simpler and quicker route to market approval. Such generics constituted 86% of prescriptions in the United States by 2013, though their market share by sales ($260 billion in 2012) is only 31% of revenues (Thayer, 2014).

One factor to consider in the regulatory requirements for early development of new therapeutic entities is the higher degree to which costs may present barriers to smaller, innovative companies. This is commonly overlooked by many who also do not recognize that such small companies (most of which fail) are the primary initial source of new therapeutics.

A second complicating factor in considering the "pharmaceutical" market sector is the diversity of products involved. The most basic expression of this is the division of drugs into "small molecules" (which currently constitute approximately two-thirds of both INDs—applications for clinical evaluation of a new drug in humans and 80% of current new drug approvals) and biotechnology products (which constitute the bulk of the remainder—biologics such as vaccines are increasing in importance). The challenges in both developing and assessing the safety of these are very different. As will also be seen, if one considers further division into therapeutic claim areas (oncology, anti-infectives, cardiovascular, CNS, etc.), the differences become even more marked. Most of what will be presented and discussed in this volume speaks to regulatory requirements for nonclinical safety assessment in the general case for either small molecules or protein therapeutics. It should be kept in mind that this general case development model never fully applies.

Additionally, there is now a significant hybrid area—combination products, which include both device and drug (small molecule or biologic) components. These will be addressed in a separate chapter of the book, though there is no single dedicated regulatory arm (such as a center within the FDA truly dedicated to only their regulation) in any major market country or such. For that reason, more exploration of regulatory considerations will be provided in the chapter on these products.

The extent of regulations and practices for drug approval causes pharmaceutical companies to spend an enormous amount of resources on developing applications, following different standards for preclinical and nonclinical programs for specific therapeutic areas, as well as time and resources to satisfy the regulatory processes for clinical trials. Because of the regulatory diversity that existed, representatives from the regulatory authorities and trade associations came together in the late 1980s and early 1990s to attempt at harmonizing the process for drug approvals. Clearly this was a daunting task. With time, however, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use has become increasingly more effective. Fortunately, the abbreviation for this very long title is ICH. Japan, Europe, and the United States represent the major pharmaceutical market for the world, and these regions have the most influence on developments within ICH and tend to follow the guidance documents that are prepared. However, other countries (rest of the world (ROW)) follow the developments within ICH

and tend to follow the guidance offered by ICH. However, it remains important, when seeking for the registration of pharmaceuticals, to be aware of local country regulations. For example, China has become a major economic force in many aspects. Placement of pharmaceutical manufacturing facilities and the marketing of drugs in China may potentially represent a significant marketing advantage to companies. With this new market area in Asia, regulatory processes are being developed; sometimes it seems at the whim of the government. With time it is hoped that China will align itself more with the processes and guidance that have been developed by ICH, FDA, and other further developed countries.

1.3 HISTORY OF MODERN THERAPEUTICS

Although, prior to the nineteenth century, preventive medicine had made some spectacular advances, for example, through nutrition (scurvy), control of infectious diseases (such as small pox, polio, and tuberculosis) and public health through sanitation, and control of childbirth fever and surgical infections using antiseptic techniques, truly therapeutic medicine was virtually nonexistent until the end of the nineteenth century.

Oliver Wendell Holmes (a physician and US Supreme Court Justice) wrote in 1860: "…. I firmly believe that if the whole material medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind—and the worse for the fishes." While there were a few effective medicines—digitalis, extract of willow bark, and quinine, for example—on balance, Holmes was quite correct, medicines did more harm than good.

The first edition of the British Pharmacopoeia (1864), which listed 311 preparations, gives an idea of the state of therapeutics at the time. Of those listed, 187 preparations were plant-derived materials and only nine of which were purified substances. Most of the plant products—lemon juice, rose hips, yeasts, etc.—lacked any components we would now regard as therapeutically relevant, but some (digitalis, castor oil, ergot, colchicum) were pharmacologically active. Of the 311 preparations, 103 were truly synthetic inorganic chemicals such as iodine, ferrous sulfate, sodium bicarbonate, and toxic salts of bismuth, arsenic, lead, and mercury, with but a few synthetic chemicals (diethyl ether and chloroform). The remainders were miscellaneous materials and a few animal products, such as lard, cantharidin, and cochineal.

For the pharmaceutical industry, the transition to an actual industry and discipline occurred late in the nineteenth century when three essential technologies came together. These were the science of biomedicine (especially pharmacology), synthetic organic chemistry, and the development of a chemical industry in Europe, coupled with a medical supplies/products trade.

Science began to be applied wholeheartedly to medicine—as to almost every other aspect of life—only late in the nineteenth century. Among the most important milestones from the point of view of drug discovery was the elaboration in 1858 of cell theory. This tremendous reductionist leap of the cell theory gave biology—and the pharmaceutical industry—the fundamental scientific underpinning it required. It is only by thinking of living systems in terms of the function of their cells that one can begin to understand how molecules affect them.

A second milestone was the birth of pharmacology as a scientific discipline when the world's first Pharmacological Institute was set up in 1874 at Dorpat (then in Germany—now in Estonia) by Rudolf Buchheim—literally by Buchheim himself, as the Institute was in his own house and funded by his estate. This was advanced by pioneers, such as Magendie and Claude Bernard, and linked to therapeutics.

Another vital spark on this road came with Louis Pasteur's germ theory of disease, proposed in Paris in 1878. A chemist in training, Pasteur's initial interest was in the process of fermentation of wine and beer and the souring of milk. He showed, famously, that airborne infection was the underlying cause and concluded that the air was actually alive with microorganisms. Particular types, he argued, were pathogenic to humans and accounted for many forms of disease including anthrax, cholera, and rabies. Pasteur successfully introduced several specific immunization procedures to give protection against infectious diseases. Robert Koch, Pasteur's rival and near-contemporary, clinched the infection theory by observing anthrax and other bacilli in the blood of infected animals.

The founder of chemotherapy—some would say the father of molecular pharmacology—was Paul Ehrlich. He invented "vital staining"—staining by dyes injected into living animals—and described how the chemical properties of the dyes, particularly their acidity and lipid solubility, influenced the distribution of dye to particular tissues and cellular structures. Thence came the idea of specific binding of molecules to particular cellular components. This led not only to Ehrlich's study of chemotherapeutic agents but also became the basis of pharmacological thinking to the present day. "Receptors" and "magic bullets" were Ehrlich's terms, though he envisaged receptors as targets for toxins rather than physiological mediators. Working in Koch's Institute, Ehrlich developed diphtheria antitoxin for clinical use, and put forward a theory of antibody action based on specific chemical recognition of microbial molecules, a work for which he won the 1908 Nobel Prize.

The first synthetic organic chemicals to be used for medical purposes were not therapeutic agents at all but rather anesthetics. Diethyl ether ("sweet oil of vitriol") was first made and described in 1540. Early in the nineteenth century, it and nitrous oxide (prepared by Sir Humphrey Davy in

1799 and found—by self-experimentation—to have stupor-inducing properties) had their usefulness as surgical anesthetics demonstrated only in the 1840s, by which time chloroform had also made its appearance. Synthetic chemistry at the time could deal only with very simple molecules, made by recipe rather than rational understanding of the underlying chemistry reasons, as our understanding of chemical processes and molecular structure was still in its infancy. The first therapeutic drug to truly come from synthetic chemistry was amyl nitrite, prepared in 1859 by Guthrie and used in treating angina by Brunton in 1864. This was the first example of a drug born in a recognizably "modern" way through the application of synthetic chemistry, physiology, and clinical medicine. This was a landmark indeed, for it was nearly 40 years before synthetic chemistry made any further significant contribution to therapeutics and not until well into the twentieth century that physiological and pharmacological knowledge began to be applied to the invention of new drugs.

During the latter half of the nineteenth century, the foundations of synthetic organic chemistry were laid, the impetus coming from work on aniline, a copious by-product of the coal–tar industry, with the discovery of how to produce a purple dye. This discovery gave birth to the synthetic dyestuffs industry, which played a major part in establishing the commercial potential of synthetic organic chemistry—a technology which later became the underpinning of the evolving pharmaceutical industry for the next century. A systematic approach to organic synthesis went hand in hand with improved understanding of chemical structure.

Despite the limited of efficacy of the pharmaceutical preparations that were available in the nineteenth century ("patent medicines"), the pharmacists trade flourished; then, as now, physicians felt themselves obligated to issue prescriptions to satisfy the expectations of their patients for some therapeutic action—or at least cause for hope. Early in the nineteenth century, a few enterprising chemists undertook the task of isolating the active substances from these plant extracts. The trend began with Friedrich Serturner, a junior apothecary in Westphalia, who in 1805 isolated and purified morphine, barely surviving a test of its potency on himself. This was the first "alkaloid," so named because of its ability to neutralize acids and form salts. This discovery in turn led to the isolation of other plant alkaloids, including strychnine, caffeine, and quinine. The recognition that medicinal plants owed their properties to their individual chemical constituents, rather than to some intangible property associated with their living nature, marks a critical point in the history of the pharmaceutical industry which can be recognized as the point of origin of two of the three roads from which the industry grew—namely, the beginnings of the "industrialization" of the pharmaceutical trade. This revelation hinted at the future and the possibility of making drugs artificially.

The first local apothecary business to move into large-scale production and marketing of pharmaceuticals was the old-established Darmstadt firm Merck founded in 1668. This development, in 1827, was stimulated by the advances in purification of natural products. Merck was closely followed in this astute business move by other German- and Swiss-based apothecary businesses, giving rise to some which later also became giant pharmaceutical companies, such as Schering and Boehringer. The American pharmaceutical industry emerged in the middle of the nineteenth century; Squibb began in 1858 with ether as its main product. The move into pharmaceuticals was also followed by several chemical companies such as Bayer, Hoechst, Agfa, Sandoz, Geigy, and others which began as dyestuffs manufacturers. The dyestuffs industry at that time was also based largely on plant products, which had to be refined and were sold in relatively small quantities, so the commercial parallels with the pharmaceutical industry were plain.

After 1870, with the crucial discovery by Kekule of the structure of benzene, the dyestuffs industry turned increasingly to synthetic chemistry as a source of new compounds, starting with aniline-based dyes. A glance through any modern pharmacopeia will show the overwhelming preponderance of synthetic aromatic compounds, based on the benzene ring structure, among the list of useful drugs. Understanding the nature of aromaticity was critical.

Thus, the beginnings of the pharmaceutical industry as we now know it, at the latest, date from about third of the 1800s, with origins in the apothecaries and patent medicine trades on the one hand and the dyestuffs industry on the other. Unfortunately, these enterprises had rather few effective products to sell (mainly inorganic compounds of varying degrees of toxicity and others most charitably described as concoctions).

Entering the 1900s, synthetic drugs had been made and tested, including the "antipyretics" and various central nervous system depressants. Chemical developments based on chloroform had produced chloral hydrate, the first nonvolatile CNS depressant, which was in clinical use for many years as a hypnotic drug. Independently, various compounds based on urea were found to act similarly, and von Mering followed this lead to produce the first barbiturate, barbitone (since renamed barbital), which was introduced in 1903 by Bayer and gained widespread clinical use as a hypnotic, tranquilizer, and antiepileptic drug—the first blockbuster. Barbitone and procaine were triumphs for chemical ingenuity but owed little or nothing to physiology or indeed pharmacology. The physiological site or sites of action of barbiturates remain unclear to this day, and their mechanism of action at the molecular level was unknown until the 1980s.

The pattern of drug discovery driven by synthetic chemistry—with biology often struggling to keep up—became the established model in the early part of the twentieth century and prevailed for at least 50 years. The balance of research in the pharmaceutical industry up to the 1970s

placed chemistry clearly as the key discipline in drug discovery, the task of biologists being mainly to devise and perform assays capable of revealing possible useful therapeutic activity among the many anonymous white powders that arrived for testing. Research management in the industry was largely in the hands of chemists. This strategy produced many successes, including benzodiazepine tranquilizers, several antiepileptic drugs, antihypertensive drugs, antidepressants, and antipsychotic drugs. The surviving practice, of classifying many drugs on the basis of their chemical structure rather than on the more logical basis of their site or mode of action (therapeutic class), stems from this era.

We have mentioned the early days of pharmacology, with its focus on plant-derived materials, such as atropine, tubocurarine, strychnine, digitalis, and ergot alkaloids, which were almost the only drugs that existed until well into the twentieth century. Despite the rise of synthetic chemistry, natural products not only remain a significant source of new drugs, particularly in the field of chemotherapy, but also in other applications. Following the discovery of penicillin by Fleming in 1929, and its development as an antibiotic for clinical use by Chain and Florey in 1938, an intense search was undertaken for antibacterial compounds produced by fungi and other microorganisms, which yielded many useful antibiotics, including chloramphenicol (1947), tetracyclines (1948), streptomycin (1949), and others. The same fungal source that yielded streptomycin also produced actinomycin D used in cancer chemotherapy. Higher plants have continued to yield useful drugs, including vincristine and vinblastine (1958), paclitaxel (or taxol, 1971), and ixabepilone (2007). Demain and Vaishnav (2011) provide an excellent review of this from the perspective of cancer chemotherapy.

Outside the field of chemotherapy, successful drugs derived from natural products include ciclosporin (1972) and tacrolimus (1993), both of which come from fungi and are used to prevent transplant rejection. Soon after came mevastatin (1976), another fungal metabolite, which was the first of the "statin" series of cholesterol-lowering drugs which act by inhibiting the enzyme HMG-CoA reductase.

Overall, the pharmaceutical industry continues to have something of an on-again, off-again relationship with natural products. They often have weird and wonderful structures that cause hardened chemists to turn pale; they are often near-impossible to synthesize, troublesome to produce from natural sources, and "optimizing" such molecules to make them suitable for therapeutic use is prone to frequent failure. But nature continues to unexpectedly provide some of our most useful drugs, and most of its potential remains untapped.

Although chemistry was the preeminent discipline in drug discovery until at least the 1970s, the seeds of the biological revolution were sown long before. Starting foremost in the field of chemotherapy, where Ehrlich defined the principles of drug specificity in terms of a specific interaction between the drug molecule and a target molecule—the "receptor site"—in the organism, although we now take it for granted that in almost all cases a highly specific chemical target molecule, as well as the "pharmacophore" or an outline portion of the drug molecule, determines what effects a therapeutic will yield, before Ehrlich no one had envisaged drug action in this way. By linking chemistry and biology, Ehrlich defined the parameters of modern drug discovery.

Despite these discoveries in Ehrlich's field, chemotherapy remained empirical rather than target directed. That said, for many years, Ehrlich's preoccupation with curing syphilis and the binding of chemical dyes, as exemplified by biological target-based drug development from the 1950s onwards, steadily shifted the industry's focus from chemistry to biology (Hill and Rang, 2012). The history of successes in the field of chemotherapy prior to the antibiotic era (Table 1.3) demonstrates the diversity of sources of new therapeutic entities. The popular image of "magic bullets"—(a phrase first used by Ehrlich in 1905)—is the essence of today's target-directed approaches to drug discovery.

More recently, as this book will show, all new categories of therapeutic entities (biotechnology-derived monoclonal antibodies, cell tissue therapies, and gene therapies) have entered use in medicine as "drugs."

1.4 THE DRUG DEVELOPMENT PROCESS

While the processes for the discovery of new potential therapeutic drugs are very diverse (Gad, 2005; Choerghade, 2006; Mathieu, 2008), once the decision is made to move a candidate compound forward to (hopefully) market approval, the general process is well defined in the components of its regulatory requirements (though with significant variability and frequent change in its details). It has many components which are beyond the scope of safety assessment, and therefore of this volume (including chemical development, clinical evaluation, and a host of regulatory actions.)

The process generally proceeds by way of getting regulatory concurrences for entering clinical trials, then proceeding through three (not strictly defined) stages of clinical trials (Phase I, Phase II, and finally Phase 3), followed by submission of a full set of documents, data, and a proposed label seeking regulatory approval for a marketing application.

The metrics of this process as it now operates make cancer the most prevalent therapeutic target for new drugs, with perhaps as many as one-third of all new drug candidates being in this claim area. Heart diseases, CNS diseases, nervous system diseases, and immune system disorders follow in order of current popularity (Table 1.4).

According to www.pharmabioingredients.com, more than 16 000 different drugs to be in development in 2006 were spread across the entire course of the development process (Table 1.5).

At the same time, the metrics of regulatory applications for the development of new drugs in the United States (where the best data is available) show a continued increase in the number of candidates entering the development process as indicated by the number of new (or original) INDs filed,

TABLE 1.3 Examples of Drugs from Different Sources

Natural Products	Synthetic Chemistry[a]	Biopharmaceuticals Produced by Recombinant DNA Technology
Antibiotics (penicillin, streptomycin, tetracyclines, cephalosporins, etc.)	Early successes include:	Human insulin (the first biotech product, registered 1982)
Anticancer drugs (doxorubicin, bleomycin, actinomycin, vincristine, vinblastine, taxol, etc.)	Antiepileptic drugs	Human growth hormone
Atropine, hyoscine	Antimetabolites	α-interferon, γ-interferon
Ciclosporin	Barbiturates	Hepatitis B vaccine
Cocaine	Bronchodilators	Tissue plasminogen activator (t-PA)
Colchicine	Diuretics	Hirudin
Digitalis (digoxin)	Local anesthetics	Blood-clotting factors
Ephedrine	Sulfonamides	Erythropoietin
Heparin		Granulocyte and granulocyte–monocyte colony-stimulating factor (G-CSF, GM-CSF)
Human growth hormone[b]		
Insulin (porcine, bovine)[b]		
Opium alkaloids (morphine, papaverine)		
Physostigmine		
Rauwolfia alkaloids (reserpine)		
Statins		
Streptokinase		
Tubocurarine		
Vaccines		

[a] Since about 1950, synthetic chemistry has accounted for the great majority of new drugs.
[b] Now largely or entirely replaced by material prepared by recombinant DNA technology.

TABLE 1.4 Potential New Drugs in US Clinical Trials by Primary Disease/Medical Use, 2005–2006

Disease/Medical Use	# of Potential New Drugs in US Clinical Trials
Cancer	5468
Mental and behavioral disorders	2397
Heart disease	2342
Rare diseases	5765
Symptoms and general pathology	4227
Nervous system diseases	2928
Immune system disorders (not including HIV/AIDS)	2578
Urinary tract and sexual organs and pregnancy	1756
Skin and connective tissue diseases	1727
Blood and lymph conditions	1654
Bacterial and fungal diseases	1591
Respiratory tract diseases	1548
Digestive system diseases	1527
Nutritional and metabolic diseases	1296
Gland- and hormone-related diseases	1216
Viral diseases	1168
Diseases or abnormalities at or before birth	1090
Injuries, poisonings, and occupational diseases	832
Muscle, bone, and cartilage diseases	699

TABLE 1.5 2006 Status of Drugs in Development

Stage	Drugs
New drug application (NDA)/biological license application (BLA) filed	482
Phase III	1179
Phase II	2622
Phase I/IND Filed	2415
Preclinical/discovery	7569
Recent product launches	2002
Total	16 269

with the proportion of these that are commercial (or traditional INDs) continuing to increase (see Table 1.6).

Also, at the same time, the rate of approval of new molecular entities has only recently recovered to levels of 30 a year for the last 2 years. This preceding multiyear "drought" finally caused recognition that the traditional/existing system of development focused on blockbusters is irretrievably broken.

1.5 STRATEGIES FOR DEVELOPMENT: LARGE VERSUS SMALL COMPANY OR THE SHORT VERSUS LONG GAME

While harmonization and societal concern for safety are driving the changes in regulatory processes for device and drug development to become more confused, strategies for

TABLE 1.6 INDs Received and Active at CDER

Calendar Year Received	Original INDs Received	Number of Active INDs at Years End	NDAs
1998	2,419	12,723	121
1999	1,763	12,584	139
2000	1,812	11,838	115
2001	1,872	10,873	98
2002	2,374	11,544	105
2003	2,120 (426 commercial)	12,661 (4,544 commercial)	109
2004	1,837 (621 commercial)	12,778 (4,827 commercial)	115
2005	1,934 (637 commercial)	13,360 (5,029 commercial)	116
2006	1,863 (713 commercial)	14,117 (5,445 commercial)	123
2007	2,589 (779 commercial)	14,566 (5,417 commercial)	124
2008	2,039 (883 commercial)	15,892 (5,962 commercial)	128
2009	1,554 (730 commercial)	9,299 (5,876 commercial)	146
2010	1,330 (601 commercial)	9,633 (5,838 commercial)	103
2011	1,404 (644 commercial)	9,883 (6,030 commercial)	105
2012	1,284 (636 commercial)	9,627 (5,966 commercial)	33 (only recorded for 3 months)
2013	1,429 (732 commercial)	10,205 (6,115 commercial)	133
2014	1,508 (782 commercial)	10,802 (6,599 commercial)	123
2015	1,564 (799 commercial)	10,973 (6,894 commercial)	146

product development and the associated nonclinical safety assessment can still be viewed in terms of broad trends.

The driving truths behind strategies in developing new drugs are:

1. Most molecules will fail. While the true success rate is certainly greater than the often quoted 1 in 10 000, it is clear that only 3–5% of those that enter initial clinical evaluation (i.e., for which an IND "opens") become marketed drugs. This rate varies depending on therapeutic class (oncology drugs having a success rate as low as 1–2% and CNS therapeutics being only somewhat higher) (Pangalos et al., 2007).
2. The cost of developing drugs is high—while not the currently quoted "average" of $1.4 billion, just getting to the point of an IND opening will cost a minimum of $2 million. One can spread out the rate of expenditure over time or shorten the required time by spending money more rapidly. But there are fixed minimums for cost and time.

Costs of development go up sharply with time/progress—subsequent to a plain vanilla first-in-man (FIM) trial, outlays come to be spoken of first in tens of millions, and (frequently) before a marketing approval filing in the hundreds of millions. Once the decision is made to develop a molecule into a drug, the process takes years. Again, one can dispute how many (from 5 to 16 years about covers the extreme range) and at no point up to the end is success (achieving marketing approval and economically successful therapeutic use) assured.

These truths conspire to produce the principal general goals behind drug development strategy:

1. Kill the losers as early as possible before too much money is spent on them.
2. Do all you can to minimize the time spent in developing a drug.

These principles produce a spectrum of strategies in the nonclinical safety assessment of drugs, best illustrated by looking at the two extreme cases.

1.5.1 Do Only What You Must

Driven by financial limitations and the plan that, at an optimal point in development (most commonly after either FIM/Phase I trials or a "proof of concept" Phase II trial), the candidate therapeutic will be licensed to or partnered with a large company, only the technical and regulatory steps necessary to

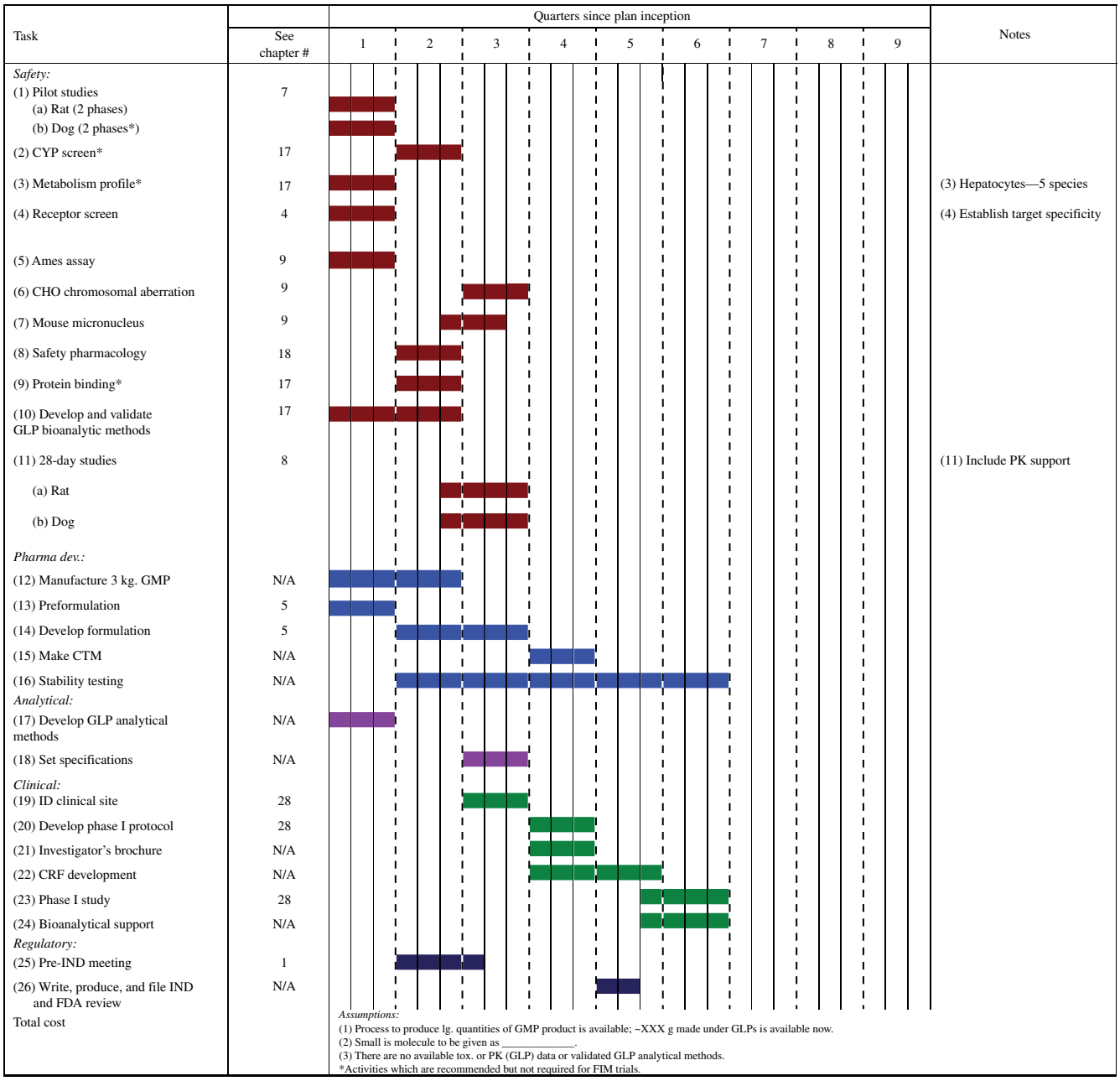

FIGURE 1.1 General case oral drug: lead through Phase I (do only what you must).

get a molecule to this point are to be performed. For those pursuing this case, the guidance provided by this book should prove essential (though not generally completely sufficient). This approach is summarized in Figure 1.1.

1.5.2 Minimize the Risk of Subsequent Failure

This is considered the traditional big company model. Studies and technical tasks are not limited to the minimum but rather are augmented by additional components. Development proceeds through a series of well-defined and carefully considered "go-no-go" decision points. This approach is summarized in Figure 1.2. Many of the additional components are either limited, non-GLP forms of studies, which will be required later (such as Ames, acute toxicity, hERGs at only one concentration, and 7 days to 4 weeks repeat-dose studies), or studies which are inexpensive and could be done later (CYP inhibitors, induction, metabolic stability, and longer than required repeat-dose toxicity studies before proceeding into Phase II). Exactly which "extra" components are included vary from company to company and frequently reflect past experiences of the organization or individuals involved.