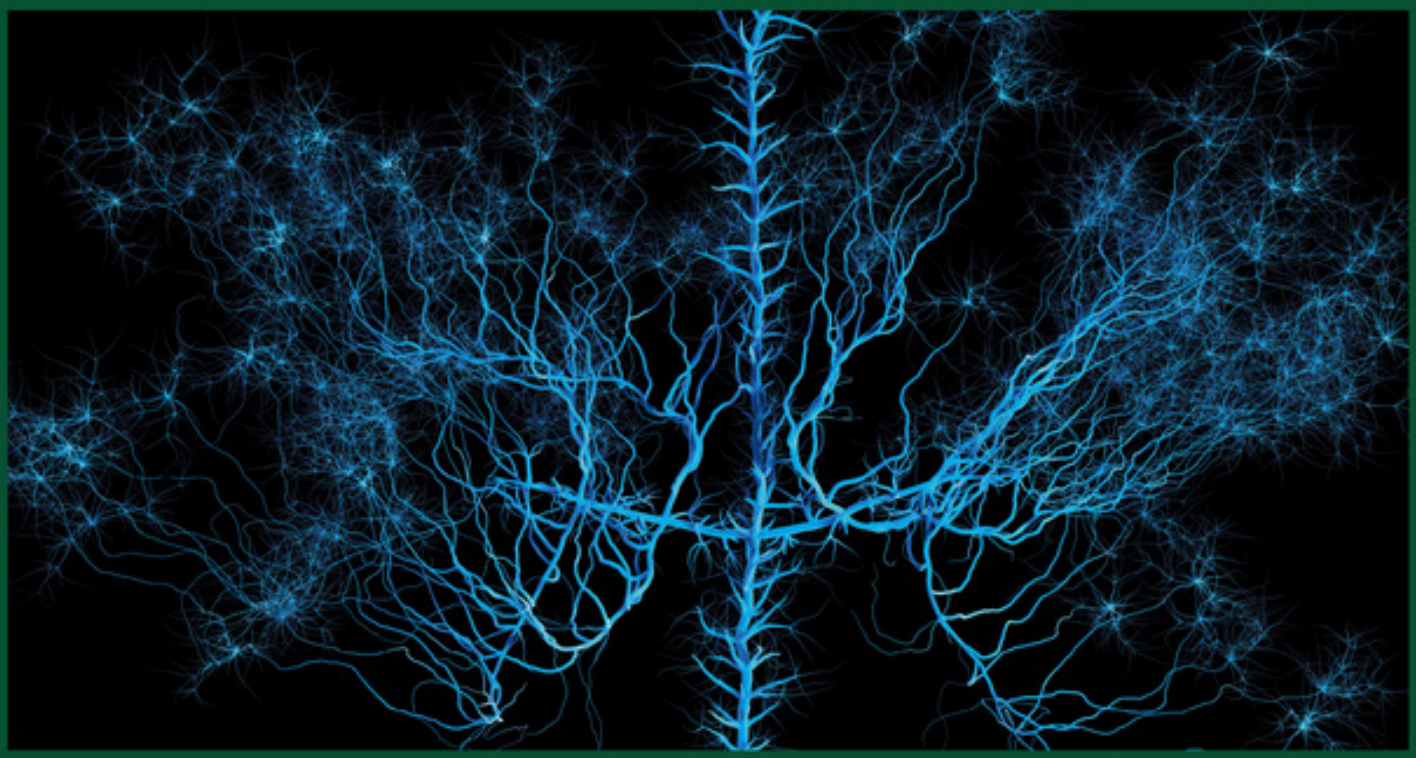
# Drug Safety Evaluation

Third Edition

*Shayne Cox Gad*



WILEY

# DRUG SAFETY EVALUATION

# DRUG SAFETY EVALUATION

3rd Edition

**SHAYNE COX GAD**

WILEY

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada



***Library of Congress Cataloging-in-Publication Data:***

Names: Gad, Shayne C., 1948– , author.
Title: Drug safety evaluation / Shayne Cox Gad.
Description: 3rd edition. | Hoboken, New Jersey : John Wiley & Sons, Inc., [2017] | Includes bibliographical references and index.
Identifiers: LCCN 2016014287| ISBN 9781119097396 (cloth) | ISBN 9781119097402 (Adobe pdf) | ISBN 9781119097419 (ePub)
Subjects: | MESH: Drug Evaluation, Preclinical | Drug Evaluation | Product Surveillance, Postmarketing
Classification: LCC RA1238 | NLM QV 771 | DDC 615/.19–dc23
LC record available at http://lccn.loc.gov/2016014287

Set in 10/12pt Times by SPi Global, Pondicherry, India

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

*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

# ACKNOWLEDGEMENT

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.

# CONTENTS

# 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.

Shayne Cox Gad
Raleigh, North Carolina

# ABOUT THE AUTHOR

**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.

# 1

# 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

*Drug Safety Evaluation*, Third Edition. Shayne Cox Gad.

**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

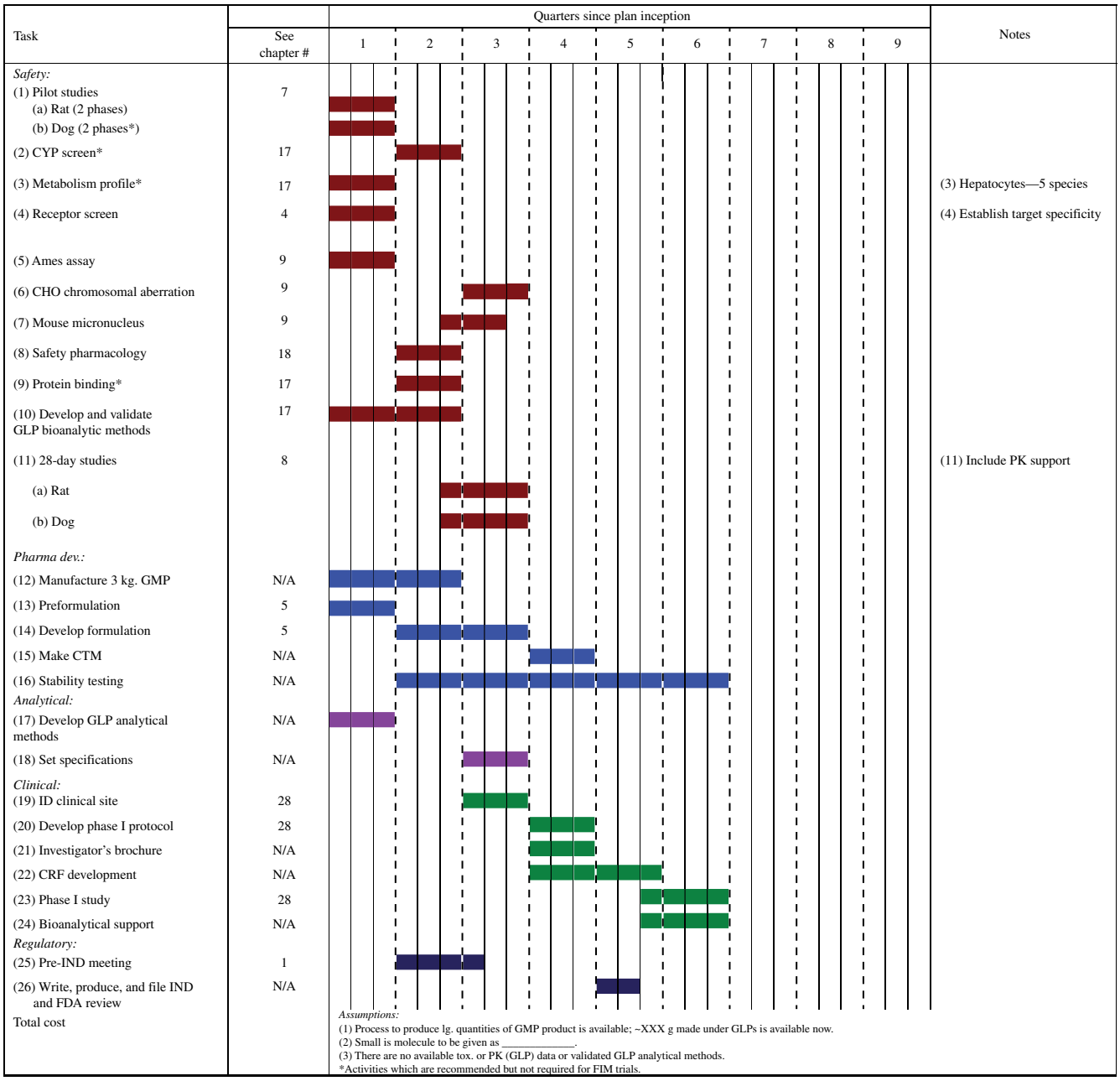
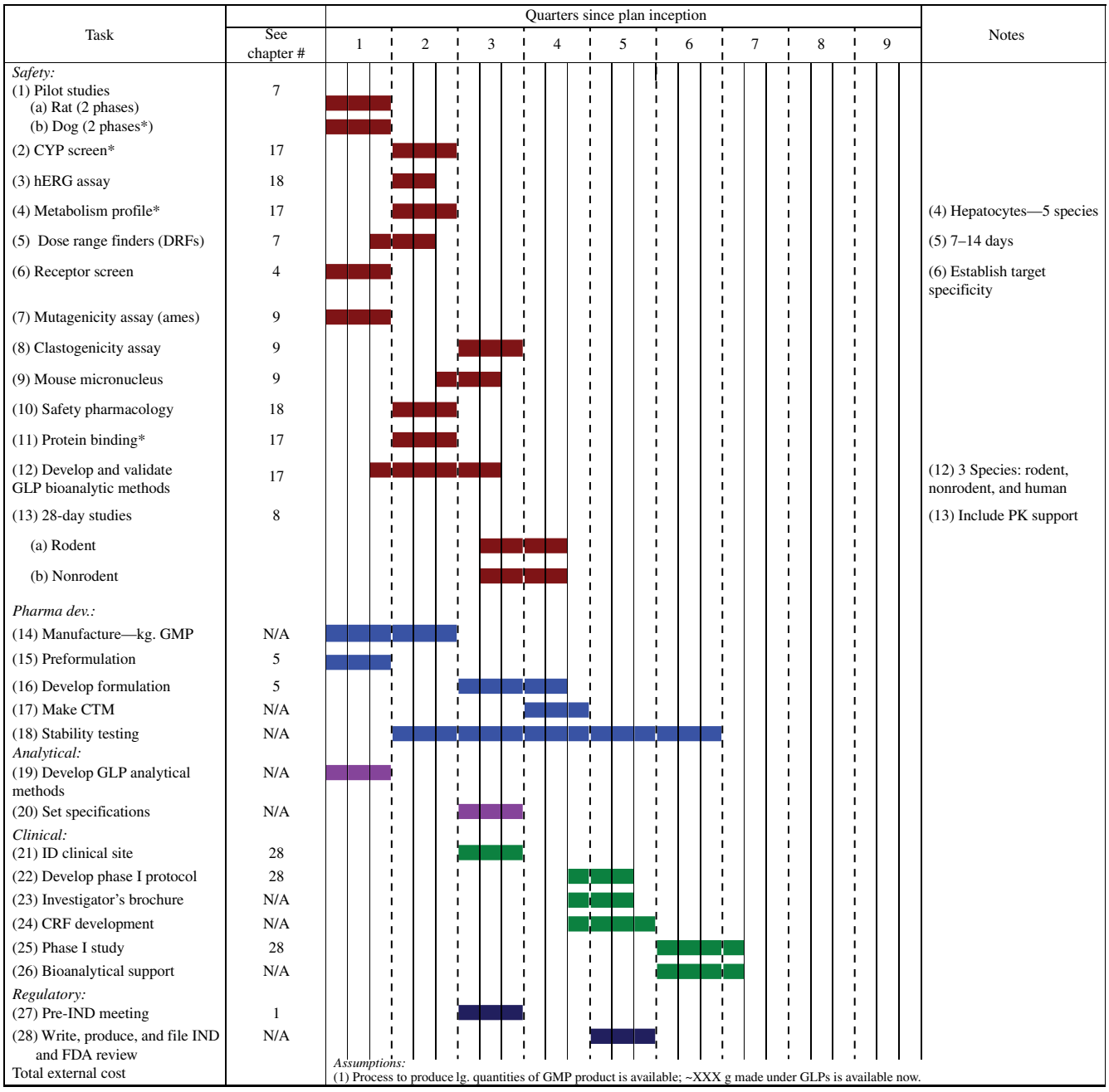



**FIGURE 1.1** General case oral drug: lead through Phase I (do only what you must).

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.




—: fill the number of Kg to be manufactured.

**FIGURE 1.2** General case oral drug: lead through Phase I (minimize risk).

The studies performed to meet regulatory nonclinical safety assessment requirements (which must be considered to include all of the supportive toxicokinetic and metabolism activities and studies) can be thought of as belonging to three major categories:

a. Those necessary to support the successful filing/opening of an IND, CTA or equivalent application, and of the subsequent FIM clinical studies.
b. Those required to support continuation of clinical evaluation and development of a drug, up to and through successful Phase III studies.
c. Those studies required to support a successful marketing approval application (NDA, BLA, or equivalent) but only required as such. This group is typically exemplified for carcinogenicity studies and the formal reproductive (as opposed to developmental) toxicity studies.

Which studies fit into what category is somewhat fluid and influenced by what patient population will be served (therapeutic claim) and the mechanism of action of the drug.

## 1.6 SAFETY ASSESSMENT AND THE EVOLUTION OF DRUG SAFETY

In the mid-nineteenth century, restrictions on the sale of poisonous substances were imposed in the United States and United Kingdom, but it was not until the early 1900s that any system of "prescription-only" medicines was introduced, requiring approval of purchase by a licensed medical practitioner. Soon afterwards, restrictions began to be imposed on what "cures" could be claimed in advertisements for pharmaceutical products and what information had to be given on the label; legislation evolved at a leisurely pace. Most of the concern was with controlling frankly poisonous or addictive substances or contaminants, not with the efficacy and possible harmful effects of new drugs.

In 1937, the use of diethylene glycol as a solvent for a sulfonamide preparation caused the deaths of 107 children in the United States, and a year later the 1906 Food and Drugs Act was revised, requiring safety to be demonstrated before new products could be marketed, as well as federal inspection of manufacturing facilities. The requirement for proven efficacy, as well as safety, was added in the Kefauver–Harris amendment in 1962 (said amendment being brought about largely by a safety issue—the thalidomide disaster in Europe).

In Europe, preoccupied with the political events in the first half of the century, matters of drug safety and efficacy were a minor concern, and it was not until the mid-1960s, in the wake of the thalidomide disaster—a disaster averted in the United States by an officer who used the provisions of the 1938 Food and Drugs Act to delay licensing approval—that the United Kingdom began to follow the United States' lead in regulatory laws. Until then, the ability of drugs to do harm—short of being frankly poisonous or addictive—was not really appreciated, most of the concern having been about contaminants. In 1959, when thalidomide was first put on the market by the German company Chemie Grünenthal, it was up to the company to decide how much research was needed to satisfy itself that the drug was safe and effective. Grunenthal made a disastrously wrong judgment (see Sjöström and Nilsson (1972) for a full account), which resulted in an estimated 10 000 cases of severe congenital malformation following the company's specific recommendation that the drug was suitable for use by pregnant women. This single event caused an urgent reappraisal on a global scale, leading to the introduction of much tighter government controls.

By the end of the 1960s, the primary planks in the regulatory platform—evidence of safety, efficacy, and chemical purity—were in place in most developed countries. Subsequently, the regulations have been adjusted in various minor ways and adopted with local variations in most countries.

In 1988, Alder and Zbinden published *National and International Drug Safety Guidelines* which set forth the wide differences in safety assessment requirements between the different nations of the world, at the time global development of a drug required multiple safety assessment programs, with a great number of repetitions of studies and attendant extra costs and increased usage of test animals.

The solution to this was that ICH paradigm which, starting in the late 1980s, sought to have a harmonized set of global requirement for all aspects of drug development (not just assessment). The safety assessment aspects were embodied primarily in the S series ICH guidelines (M4 which sets forth the overall structure of nonclinical requirements being an exception). This did serve to largely standardize ("harmonize") global requirements, with minor differences.

As the rest of this book will make clear, this system is now fraying a bit at the edges.

Recent additions of new guideline topic areas (e.g., immunotoxicology), revisions to existing guidelines (on genotoxicity and biotechnology), regional guideline responses to recent occurrences (the case in point being the failed TGN1412 FIM trial and the resulting two EMA special guidances issued in response to it), as well as differences in requirements for different therapeutic classes have reversed the harmonization trend.

Just as this book was being submitted for publication, reports have been released of a Phase I trial of BIA 10–2474, a fatty acid amide hydrolase (FAAH) inhibitor targeted at the body's endocannabinoid system and intended to treat mood anxiety and movement coordination issues, going drastically wrong. Six males received repeat doses of the drug after 84 others had shown no marked effects. One was first pronounced brain dead but subsequently died, while three of the other five have also shown serious effects, perhaps irreversible.

The oral small molecule drug was made by the Portuguese company Bial, but clinical tests were performed in a commercial CRO in France (BioTrial). A meta-analysis of noncancer Phase I drug trials, published last year in The British Medical Journal, found serious adverse events in only 0.31% of participants and no deaths (Chan, 2016).

## 1.7 THE THREE STAGES OF DRUG SAFETY EVALUATION IN THE GENERAL CASE

Nonclinical safety assessment studies fall into three categories, as will be examined in detail in the remainder of this book. These are:

1. IND Enabling ("FIM"): the studies necessary to support the initiation of clinical trials in human beings. These are generally as specified in ICH M3, and this is the most common and numerous of all the three categories.

2. To support continued clinical development: as clinical development proceeds, longer repeat-dose drug studies must be performed, reproductive and developmental toxicology studies must be done, and other ancillary studies are required.
3. To support filing for marketing approval: the final studies generally required to support marketing of drugs—such as carcinogenicity.

Which studies fall into each of these categories, and exactly what studies must be done to support the development of a drug for a specific therapeutic claim, is extremely variable. The general case—much as specified in ICH M3(R2)—gives us a starting place for understanding what must be done.

At the same time, the image of the pharmaceutical industry in society is problematic (even more so in 2015 with well-publicized incidences of firms buying marketing rights to established small molecule drugs only to escalate prices 10–100-fold). The costs and economics of development are complex and not well understood, (Greider, 2003; Angell, 2004; Goozner, 2004; Petersen, 2008) while the role and abilities of regulatory agencies are equally misunderstood (Hawthorne, 2005).

But the general case really applies to the simplest oral drug intended for chronic use, and more often than not, doesn't apply. In fact, it may never fully apply.

## REFERENCES


Alder S, Zbinden G. (Eds.) (1988) *National and International Drug Safety Guidelines*. M.T.C. Verlag, Zollikon.

Angell M. (2004) *The Truth about the Drug Companies: How They Deceive Us and What to Do About It*. Random House, New York.

Chan S. (2016) 6 Hospitalized, one of them brain-dead, after drug trial in France. *The New York Times*, January 16, 2016: B2.

Choerghade MS. (Ed.) (2006) *Drug Discovery and Development*. John Wiley & Sons, Inc., Hoboken, NJ.

Demain AL, Vaishnav P. (2011) Natural products for cancer chemotherapy. *Microb. Biotechnol.* 4(6):687–699.

Drugs.com (2014) *U.S. Pharmaceutical Sales—Q4 2013*. The Drugsite Trust, Auckland, New Zealand. Available at: http://www.drugs.com/stats/top100/2013/sales (accessed May 26, 2016).

Gad SC. (Ed.) (2005) *Drug Discovery Handbook*. John Wiley & Sons, Inc., Hoboken, NJ.

Gad SC. (2011) *Safety Evaluation of Pharmaceuticals and Medical Devices: International Regulatory Guidelines*, 1st Ed. Springer, New York.

Goozner M. (2004) *The $800 Million Pill: The Truth Behind the Cost of New Drugs*. University of California Press, Berkley, CA.

Greider K. (2003) *The Big Fix: How the Pharmaceutical Industry Rips Off American Consumers*. Public Affairs, New York.

Hawthorne F. (2005) *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. John Wiley & Sons, Inc., Hoboken, NJ.

Hill R, Rang HP. (Eds.) (2012) *Drug Discovery & Development: Technology in Transition*. Churchill Livingstone, New York.

Mathieu M. (2008) *New Drug Development: A Regulatory Overview*, 8th Ed. Parexel International, Waltham, MA.

Pangalos MN, Schecter LE, Hurko O. (2007) Drug development for CNS disorders: strategies for balancing risk and reducing attrition. *Nat. Rev. Drug Discov.* 6(7):521–532.

Petersen M. (2008) *Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs*. Sarah Crichton Books, New York.

PMLive (2015) *Top 25 Pharma Companies by Global Sales*. Accessible at: http://www.pmlive.com/top_pharma_list/global_revenues. Last accessed 8-9-2016.

Sjöström H, Nilsson R. (1972) *Thalidomide and the Power of the Drug Companies*. Penguin, New York.

Thayer AM. (2014) 30 years of generics: the door that legislation unlocked for generic drugs three decades ago has blown wide open. *Chem. Eng. News*. 92(39):8–16.

# 2

# REGULATION OF HUMAN PHARMACEUTICAL SAFETY: ROUTES TO HUMAN USE AND MARKET

## 2.1 INTRODUCTION

The safety of pharmaceutical agents, medical devices, and food additives is the toxicology issue of the most obvious and longest-standing concern to the public. A common factor among the three is that any risk associated with a lack of safety of these agents is likely to affect a very broad part of the population, with those at risk having little or no option as to undertaking this risk. Modern drugs are essential for life in our modern society, yet there is a consistent high level of concern about their safety.

This chapter examines the regulations which establish how the safety of human pharmaceutical products is evaluated and established in the United States and the other major international markets. As a starting place, the history of this regulation will be reviewed, and the current organizational structure of the Food and Drug Administration (FDA) will be briefly reviewed, along with the other quasigovernmental bodies that also influence the regulatory processes. The current structure and context of the regulations in the United States and overseas will also be presented. From this point the general case of regulatory product development and approval will be presented. Nonclinical safety assessment study designs will be presented. The broad special case of biotechnology-derived therapeutic products and environmental concerns associated with the production of pharmaceuticals will be briefly addressed. The significant changes in regulation brought about by harmonization are also reflected.

As an aid to the reader, appendices are provided at the end of this book: a codex of acronyms that are used in this field, followed by a glossary which defines some key terms.

## 2.2 BRIEF HISTORY OF US PHARMACEUTICAL LAW

A synopsis of the history of US drug legislation is presented in Table 2.1. Here we will review the history of the three major legislative acts covering pharmaceuticals.

### 2.2.1 1906: Pure Food and Drug Act

As so eloquently discussed by Temin (1980), the history of health product legislation in the United States largely involves the passage of bills in Congress which were primarily in response to public demand. In 1902, for example, Congress passed the Biologics Act in response to a tragedy in St. Louis where 10 children had died after being given contaminated diphtheria toxins. Interestingly, the background that led to the passage of the first Pure Food and Drug Act in 1906 had more to do with food processing than drugs. The conversion from an agrarian to an urban society fostered the growth of a food-processing industry that was rife with poor practice. Tainted and adulterated food was commonly sold. Practices were sensationalized by the muckraking press, including books such as *The Jungle* by Upton Sinclair.

In the early debates in the US Congress on the Pure Food and Drug Act (passed in 1906), there was little mention of toxicity testing. When Harvey Wiley, chief of the Bureau of Chemistry, Department of Agriculture and driving force in the enactment of this early law, did his pioneering work (beginning in 1904) on the effects of various food preservatives on health, he did so using only human subjects and with no prior experiments in animals (Anderson, 1958). Ironically, work that led to the establishment of the FDA

*Drug Safety Evaluation*, Third Edition. Shayne Cox Gad.

**TABLE 2.1 Important Dates in US Federal Drug Law**

| Year | Event |
|---|---|
| 1902 | Passage of the Virus Act, regulating therapeutic serums and antitoxins. Enforcement by the Hygienic Laboratory (later to become the National Institutes of Health (NIH)), Treasury Department |
| 1906 | Passage of Pure Food Act, including provisions for the regulations of drugs to prevent the sale of misbranded and adulterated products. Enforcement by the Chemistry Laboratory, Agriculture |
| 1912 | Passage of the Sherley Amendment. Specifically outlawed any false label claims as to curative effect |
| 1927 | Bureau of Chemistry renamed the Food, Drug, and Insecticide Administration |
| 1931 | Renamed again to Food and Drug Administration |
| 1938 | Passage of the Food, Drug, and Cosmetic Act. Superseded the law of 1906. Required evidence of safety, for example, studies in animals. Included coverage of cosmetics and medical devices. Specifically excluded biologics |
| 1944 | Administrative Procedures Act, codifying public health laws: included provision that for a biological license to be granted, a product must meet standards for safety, purity, and potency. NIH also given the responsibility for developing biologics not developed by the private sector |
| 1945 | Amendment to the 1936 Act requiring that the FDA examine and certify for release each batch of penicillin. Subsequently amended to include other antibiotics |
| 1949 | Publication of the first set of criteria for animal safety studies. Following several revisions, guidelines published in 1959 as Appraisals Handbook |
| 1951 | Passage of Durham–Humphrey Amendment. Provided the means for manufacturers to classify drugs as over the counter (not requiring prescription) |
| 1953 | Transfer of FDA to the Department of Health, Education, and Welfare (HEW) from Agriculture (now the Department of Health and Human Services) |
| 1962 | Passage of major amendments (the Kefauver bill) to the 1938 FDCA, which required proof of safety and effectiveness (efficacy) before granting approval of New Drug Applications. Required affirmative FDA approval |
| 1968 | FDA placed under the Public Health Service of HEW |
| 1970 | Controlled Substance Act and Controlled Substances Import and Export Act. Removed regulation of drug abuse from FDA (transferred to the Drug Enforcement Agency) and provided for stringent regulation of pharmaceuticals with abuse potential |
| 1972 | Transfer of authority to regulate biologics transferred from NIH to FDA. The NIH retained the responsibility of developing biologics |
| 1973 | Consumer Product Safety Act, leading to the formation of separate Consumer Product Safety Commission, which assumes responsibilities once handled by the FDA's Bureau of Product Safety |
| 1976 | Medical Device Amendment to the FDCA requiring for devices that not only effectiveness be proven but also safety |
| 1979 | Passage of the Good Laboratory Practices Act |
| 1983 | Passage of the first Orphan Drug Amendment to encourage development of drugs for small markets |
| 1984 | Drug Price Competition and Patent Term Restoration Act intended to allow companies to recover some of the useful patent life of a novel drug lost due to the time it takes the FDA to review and approve. Also permits the marketing of generic copies of approved drugs |
| 1985 | The "NDA rewrite" final rule. An administrative action streamlining and clarifying the New Drug Application process. Now embodied in 21 CFR 314 |
| 1986 | The US Drug Export Amendment Act of 1986. Permitted the export of drugs outside the United States prior to approval for the US market |
| 1987 | The "IND rewrite" final rule. "…to encourage innovation and drug development while continuing to assure the safety of (clinical) test subjects." Federal Register 52:8798, 1987. Now embodied in 21 CFR 312 |
| 1992 | Prescription Drug User Fee Act. Established the payment of fees for the filing of applications (e.g., IND, NDA, PLA, etc.) |
| 1994 | Orphan Drug Amendment |
| 1997 | The Food and Drug Administration Modernization Act: to streamline the drug and device review and approval process |
| 2002, 2007 and 2012 | The Food and Drug Administration Modernization Act Amendments |

*Note*: Laws and amendments that have covered other aspects of FDA law, such as those governing food additives (e.g., FQPA), are not included in this table.

would probably not have been permitted under the current guidelines of the agency. Wiley's studies were not double blinded, so it is also doubtful that his conclusions would have been accepted by the present agency or the modern scientific community. Legislation in place in 1906 consisted strictly of a labeling law prohibiting the sale of processed food or drugs that were misbranded. No approval process was involved and enforcement relied on postmarketing criminal charges. Efficacy was not a consideration until 1911, when the Sherley Amendment outlawed fraudulent therapeutic claims.

### 2.2.2 1938: Food, Drug, and Cosmetic Act

The present regulations are largely shaped by the law passed in 1938. It will, therefore, be discussed in some detail. The story of the 1938 Food, Drug, and Cosmetic Act (FDCA) actually begins in 1933. Franklin D. Roosevelt had just won his first election and installed his first cabinet. Walter Campbell was the chief of the FDA, reporting to Rexford Tugwell, the Undersecretary of Agriculture. The country was in the depths of its greatest economic depression. This was before the therapeutic revolution wrought by antibiotics in the 1940s, and medicine and pharmacy as we know them in the 2010s were not practiced. Most medicines were, in fact, self-prescribed. Only a relatively small number of drugs were sold via physicians' prescription. The use of so-called patent (because the ingredients were kept secret) preparations was rife, as was fraudulent advertising. Today, for example, it is difficult to believe that in the early 1930s a preparation such as Radithor (nothing more than a solution of radium) was advertised for treatment of 160 diseases. It is in this environment that 1 day in the winter of 1933, Campbell delivered a memo to Tugwell on an action level of an insecticide (lead arsenite) used on fruits. Tugwell briskly asked why, if the chemical was so toxic, was it not banned outright. He was amazed to find out from Campbell that the agency had no power to do so.

The 1906 law was designed to control blatantly misbranded and/or adulterated foods and drugs and relied on post facto criminal charges for enforcement. Safety and efficacy were not an issue so long as the product was not misbranded with regard to content. Premarketing review of a drug was an unknown practice. Thus, attempts at rewriting the old 1906 law to include control of bogus therapeutic claims and dangerous preparations proved to be unsatisfactory. Paul Dunbar of the FDA suggested to Campbell that an entirely new law was needed. A committee of FDA professionals and outside academic consultants drafted a new bill, which immediately ran into trouble because no one in Congress was willing to sponsor it. After peddling the bill up and down the halls of Congress, Campbell and Tugwell convinced Senator Royal Copeland of New York to sponsor the bill. Unknowingly at the time, Copeland put himself in the eye of a hurricane that would last for 5 years.

The forces that swirled around Copeland and the Tugwell bill (Senate bill S.1944) were many. First was the immediate and fierce opposition from the patent medicine lobby. Flyers decried S.1944 as everything from a communist plot to un-American, stating it "would deny the sacred right of self-medication." In opposition to the patent trade organizations were two separate but unlikely allies: a variety of consumer advocacy and women's groups (such as the American Association of University Women, whose unfaltering support for the bill eventually proved critical to passage) and the mainline professional organizations. Interestingly, many of these organizations at first opposed the bill because it was not stringent enough. There were also the mainline professional pharmacy and medical organizations (such as the American Medical Association (AMA) and the American Association of Colleges of Pharmacy) whose support for the bill ranged from neutral to tepid, but did grow over the years from 1933 to 1938.

Secondly, there was the basic mistrust on the part of Congress toward Tugwell and other "New Dealers." At the same time, Roosevelt gave the measure only lukewarm support at best (legend has it that if it had not been for the First Lady, Eleanor, he would have given it no support at all) because of his political differences with Royal Copeland.

Thirdly, there was a considerable bureaucratic turf war over the control of pharmaceutical advertising. Finally, despite all efforts of the various lobbying groups, there was no popular interest or support for the bill. By the end of the congressional period, S.1944 had died for lack of passage.

The next 5 years would see the introduction of new bills, amendments, and competing measures, as well as committee meetings and hearings, lobbying, and House/Senate conferences. The details of this parliamentary infighting make for fascinating history but are outside the scope of this book. The reader is referred to an excellent history of this period, *Food and Drug Legislation in the New Deal* (Jackson, 1970).

The FDA was surprised by the force and depth of the opposition to the bill. The proposed law contained a then-novel idea that a drug was misbranded if its labeling made any therapeutic claim which was contrary to general medical practice and opinion. The definition of a drug was broadened to include devices used for medical purposes.[1] *Adulteration* was defined as any drug product dangerous to health when used according to label directions. The patent manufacturers charged that the new bill granted too much discretionary power to a federal agency and that no manufacturer could stay in business except by the grace of the Department of Agriculture, a charge that may have been correct. In response to the patent trade lobbying effort, the FDA launched its own educational drive consisting of radio spots, displays (such as

[1] The use of a broad definition of what constitutes a drug for regulatory purposes is a precedent that remains in place today. For example, the computer software used in diagnostic systems is considered to be a pharmaceutical for purposes of regulation.

the sensationalized Chamber of Horrors exhibition, in which the toxicity of a variety of useless medicines was clearly displayed), mimeographed circulars, speaking engagements, posters, etc.

Ruth Lamb, FDA information officer at the time, was perhaps one of the hardest working and most quotable of the FDA staffers working the street at the time. For example, in reference to one of the counter bills that had language similar to the original Copeland bill, but with extremely complicated enforcement provisions, Ruth Lamb called it "an opus for the relief of indigent and unemployed lawyers." She once described the Bailey amendment, which would have made proprietary drugs virtually immune to multiple seizures, as permitting the "sale of colored tap water as a cure for cancer…unless arsenic was added to each dose making [it] immediately dangerous." After 1934, however, the educational efforts of the FDA were greatly attenuated by federal laws prohibiting lobbying by federal agencies.

With the autumn of 1937 came the beginnings of the oft-told elixir of sulfanilamide incident, which remains one of the nation's worst drug tragedies. The Massengill Company was not one of the industry giants, but neither was it a "snake oil peddler." The company's chief chemist, Harold Watkins, was simply trying to develop a product and, in fact, did so in a manner consistent with the norms of the time. There was a perceived need for a liquid form of sulfanilamide, but it was difficult to dissolve. Then, Watkins hit upon diethylene glycol (at 72%) for use as a solvent. No toxicity tests were performed on the finished product, although the product did pass through the "control lab" where it was checked for appearance, fragrance, and consistency.

The first reports of human toxicity occurred in October 1937 when Dr. James Stevenson of Tulsa requested some information from the AMA because of six deaths in his area that were attributable to the elixir. At the time, no product of Massengill stood accepted by the Council on Pharmacy and Chemistry, and the Council recognized no solution of sulfanilamide. The AMA telegraphed Massengill, requesting samples of the preparation for testing. Massengill complied. The test revealed the diethylene glycol to be the toxic agent, and the AMA issued a general warning to the public on October 18, 1937. In the meantime, the FDA had become aware of the deaths and launched an investigation through its Kansas City station. By October 20, when at least 14 people had died, Massengill wired the AMA to request an antidote for their own product. By the end of October, at least 73 people had died, and another 20 suspicious deaths were linked to the drug. Had it not been for the response of the FDA, more deaths may have occurred. The agency put its full force of field investigators (239 members) on the problem and eventually recovered and accounted for 99.2% of the elixir produced. Massengill fully cooperated with the investigation and in November published a public letter expressing regret over the matter, but further stating that no law had been broken. In fact, the company was eventually convicted on a long list of misbranding charges and fined a total of $26,000 (the largest fine ever levied under the 1906 law).

The Massengill incident made the limits of the 1906 law quite clear. Because there were no provisions against dangerous drugs, the FDA could move only on the technicality of misbranding. The term *elixir* was defined by the US Pharmacopeia (USP) as "a preparation containing alcohol," which elixir of sulfanilamide was not. It was only this technicality that permitted the FDA to declare the "elixir" misbranded, to seize the inventory, and to stop the sale of this preparation. If it had been called *solution of sulfanilamide*, no charges could have been brought.

The extensive press coverage of the disaster became part of the national dialogue. Letters poured into congressmen demanding action to prevent another such tragedy. Medical and pharmacy groups and journals insisted that a new law was required. Congress was in special session in November 1937 and did not need to be told about the tragedy. Copeland and Representative Chapman (of Kentucky) pressed resolutions calling for a report from the FDA on the tragedy. When issued, the FDA report stunned Congress, not only because of the human disaster but also because it made apparent that even had the bill then before Congress been law, the entire tragedy would still have occurred because there were no provisions for toxicity testing before new drugs entered the market. By December 1937 a new bill, S.3037, was introduced which stated that manufacturers seeking to place new drugs on the market would be required to supply records of testing, lists of components, descriptions of each manufacturing process, and sample labels. Drugs would require certification by the FDA before sale was permitted. A similar bill was introduced in the House by Chapman, although the issues of which agency was to control advertising of drugs still festered in the House. In January 1938, debate started on the Wheeler–Lea bill, which would ensure that all controls over drug advertising would remain with the Federal Trade Commission (FTC). Despite strong opposition by the FDA, the Wheeler–Lea bill was signed into law March 1938. While the loss of advertising control was a blow to the FDA, the Wheeler–Lea bill did facilitate the passage of the new food and drug law.

With the issue of advertising controls settled, the Copeland–Chapman bill faced one last hurdle. Section 701, which had been added in committee, provided for appeal suits that could be entered in any federal district court to enjoin the agency from enforcing new regulations promulgated as a result of the Act. Interestingly, this issue had more to do with foods than drugs, as its major focus was with acceptable tolerance limits for insecticides in food. The new bill defined an *adulterated food* as one containing any poison. However, because efforts to remove insecticides from fresh fruits and vegetables had never been completely

successful, the Secretary of Agriculture needed this power to set tolerance levels. Allies of food producers tried to introduce provisions in the new bill that provided methods for stalling a tolerance regulation with rounds of appeals. The bill passed the House despite such provisions (Section 701) and despite the resistance of consumer groups and the FDA, and went into joint committee. Roosevelt, in one of his rare efforts to support the FDA, made it clear that he would not accept the bill with such a cumbersome appeals process. The resulting compromise was an appeals process which limited the new evidence that could be introduced into one of the 10 circuit courts. Other provisions regarding labeling were also rectified in joint committee. In May 1938, S.3073 passed by unanimous vote. Both chambers ratified the joint committee report, and Franklin Delano Roosevelt signed the new law in June of 1938.

A historical note to this story was that Royal Copeland did not live to see his measure passed. In May 1938, he collapsed on the Senate floor. His death occurred 1 month before President Roosevelt signed his bill into law.

### 2.2.3 1962: Major Amendment

The 1938 law very much changed the manner in which Americans purchased pharmaceutical agents. In effect, it changed the pharmaceutical industry from a traditional consumer product industry to one in which purchases were made as directed by a third party (the physician). In 1929, ethical pharmaceuticals (prescription drugs) comprised only 32% of all medicines. By 1969 this was up to 83% (Temin, 1980). This led to a peculiar lack of competition in the ethical market. In 1959, Senator Estes Kefauver initiated his now-famous hearings on the drug industry. Interestingly, almost 30 years later, Senator Edward Kennedy had hearings on exactly the same matter. In 1961, Kefauver submitted a proposed legislation to amend the 1938 Act in such a way as to increase FDA oversight of the drug industry. The proposed amendment contained two novel propositions. The first was compulsory licensing, which would have required, for example, company "A" to license (with a royalty of no greater than 8% of sales) and company "B" to market a drug patented by company "A." Company "A" would have only 3 years' exclusivity with its patent. The second novel provision was that new drugs had to be not only "safe" but also "efficacious." There was not a ground swell of support for this legislation. When it was reported out of committee, it had been rewritten (including the removal of the licensing requirement) to the point that even Kefauver refused to support it. The Kennedy administration wanted new legislation but did not specifically support the Kefauver bill; rather it introduced its own legislation, sponsored by Representative Orren Harris of Arkansas, and also with little support.

As in 1938, a tragic incident would again intercede in the legislative process: 1961 would see the development of the thalidomide tragedy. An antianxiety agent marketed in Europe, thalidomide, was prescribed for pregnancy-related depression and nausea (or "morning sickness") and taken by countless women. At about the same time, phocomelia, a birth defect marked by the imperfect development of arms and legs, appeared in Europe. Thalidomide was eventually determined to be the causative teratogen in 1961 and was subsequently taken off the European market. The William S. Merrell Company had applied for a New Drug Application (NDA) for thalidomide in the United States in 1960. It was never approved because the FDA examiner, Dr. Frances Kelsey, had returned the application for lack of sufficient information. Eventually, the company withdrew the application. Senator Kefauver's staff had uncovered the thalidomide story as it was unfolding and had turned its findings over to the *Washington Post*. The *Post* reported the episode under the headline "Heroine of the FDA Keeps Bad Drug off the Market" in July 1962, 3 days after the Kefauver bill was reported out of committee. Needless to say, the news created public support for the bill, which was sent back to committee and reported our again with new language in August 1962. The Kefauver–Harris bill was signed into law in October 1962. It was demonstrated after the fact that thalidomide was teratogenic in the rabbit; out of the episode grew the current practice of testing new human pharmaceuticals for teratogenicity in two species, one generally being the rabbit.

The 1962 Drug Amendment made three major changes in the manner in which new drugs could be approved (Merrill, 1994). First, and perhaps the most important, was that it introduced the concept of effectiveness into the approval process. An NDA had to contain evidence that the drug was not only safe but also effective. The 1938 law contained no such specification. The effectiveness requirement necessitated that a drug company had to do more extensive clinical trials. The new law required that a company apply to the FDA for approval of its clinical testing plan under an Investigational New Drug Application (INDA). No response from the FDA was deemed to be acceptance. As each level of clinical testing came to require FDA review and approval, the new law made the FDA an active partner in the development of all drugs.

The second major change enacted under the 1962 law was the change in the approval process from premarket notification to a premarket approval system. Under the terms of the 1938 law, an NDA would take effect automatically if the FDA did not respond. For example, the only reason thalidomide was not approved was because Dr. Kelsey returned the application to the sponsor with a request for more information. In contrast, the 1962 law required affirmative FDA action before a drug could be put on the market. Under the terms of the 1962 amendments, the FDA was also empowered to withdraw NDA approval and remove a drug from the market for a variety of reasons, including new evidence that the product was unsafe or that the sponsor had

misrepresented or underreported data. The basic nonclinical safety testing regimen which currently applies was developed and adapted in that time frame (Goldenthal, 1968).

The third major change enlarged the FDA's authority over clinical testing of new drugs. Thus, not only was evidence of effectiveness required, but Section 505(d) of the Act specified the types of studies required. "Substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations by a qualified expert." In meeting the statutory requirement for setting standards of clinical evidence, the FDA has become highly influential in the design of drug testing regimens (Merrill, 1994). Interestingly, discussed in detail by Hutt (1987), the FDA was initially quite unprepared for this new level of responsibility. It was not until 1973 that audited regulations on the determination of safety and effectiveness were put into place (these were, in fact, approved by the Supreme Court). While there have been several procedural changes (e.g., the 1985 Investigational New Drug (IND) rewrite) and additions (e.g., the 1988 IND procedures for life-threatening disease treatment), there have actually been no major changes in the law through 1992 with Prescription Drug User Fee Act (PDUFA) and 1997 with Food and Drug Administration Modernization Act (FDAMA) (amended in 2002, 2007, and 2012).

We must interject with an interesting historical aside at this point. Despite its reputation, thalidomide made a bit of a comeback in the 1990s (Blakeslee, 1998). Among other properties, thalidomide has been shown to have good anti-inflammatory properties, due to the fact that it apparently decreases the synthesis and/or release of tissue necrosis factor.

### 2.2.4 1992, 1997, 2002, 2007, and 2012: PDUFA and FDAMA

The history of pharmaceutical regulations has been dominated by two oft-opposing schools of thought: the need to provide the citizenry with effective medicaments and the need to protect the consumer from unsafe and misbranded products. The reader is referred to Peter B. Hutt's in-depth reviews (Hutt, 1983a, b) on the subject. For example, the very first federal drug legislation in the United States was the Vaccine Act of 1813, which mandated the provision of the smallpox vaccine to the general public. In the modern era, legislative debate could be further defined as the constant swing back and forth on these two issues (Hutt, 1983a, b), that is, safety versus development costs. In 1963, for example, Senator Hubert Humphrey presided over hearings on the FDA's implementation of the Drug Amendment of 1962. The FDA came under substantial criticism for failure to take strong action to protect the public from dangerous drugs. Eleven years later (1974), Senator Edward Kennedy conducted hearings addressing exactly the same issue. Commissioner Schmidt pressed the point that the FDA is under constant scrutiny regarding the approval of "dangerous" drugs, but no hearing had ever been conducted (up to that time) on the failure of the FDA to approve an important new therapy.

The next decade and a half saw a proliferation of work that analyzed the impact of regulation on competitiveness and the introduction of new therapies (see Hutt (1983b) for a complete review). This included Grabowski and Vernon's work (1983), which concluded that regulation had significant adverse effect on pharmaceutical innovation. This examination of the cost of regulation continued into the 1990s. In a meticulous and well-researched study, DiMasi et al. (1994) reported that throughout the 1980s, the number of INDAs was decreasing and the new drug application success rate was also dropping, while the length of time between discovery and approval was increasing. Clearly this is a situation that could not go on forever. The reported cost of developing a new drug has risen from $54 million (US) in 1976 to $2.558 billion (US, with $1.395 billion out of pocket and $1.163 billion in time cost) in 2014 (DiMasi et al., 1991; Tufts, 2014). Members of the pharmaceutical industry and the biotechnology industry were becoming increasingly alarmed by the negative synergy caused by increased costs and increased time to market. In 1991, Dranove published an editorial examining the increased costs and decreased product flow that resulted from the 1962 amendment. He made the observation that European requirements are less stringent than those of the United States, yet the Europeans did not seem to be afflicted by a greater number of dangerous drugs (see Table 1.2). Yet, if one looks at an analysis of worldwide withdrawals for safety from 1960 to 1999 (Fung et al., 2001), one sees that of 121 products identified 42.1% were withdrawn from European markets alone, then 5% from North America, 3.3% from Asia Pacific, and 49.6% from multiple markets. The top five safety reasons for withdrawal were hepatic (26.2%), hematologic (10.5%), cardiovascular (8.7%), dermatologic (6.3%), and carcinogenic (6.3%) issue.

In an age of decreasing regulatory recourses, the FDA (as well as the Congress) was under increasing pressure to review and release drugs more quickly. In response, the Congress passed the 1992 PDUFA. Under the terms of this Act, companies would pay a fee to the agency to defray costs associated with application review. They would supposedly provide the FDA with the resources available to decrease application review time. In return, companies were guaranteed a more rapid review time. By all accounts, PDUFA has been successful. In 1992 (the year PDUFA was passed), 26 NDAs were approved, requiring on average 29.9 months for data review, while in 1996, 53 new drug (or biological) products were approved, each requiring an average of 17.8 months of review time. PDUFA was successful in decreasing review times, but has not really streamlined the procedures.

The acquired immune deficiency syndrome (AIDS) activist community was particularly vocal and effective in demanding more rapid approvals and increased access to therapies. There was also demand for FDA reform on a number of other fronts (e.g., medical devices, pediatric claims, women and minority considerations, manufacturing changes, etc.). In 1993 the House Commerce Committee on Oversight and Investigations, chaired by John Dingel (D-MI), released a comprehensive investigation and evaluation of the FDA entitled *Less than the Sum of its Parts*. The report was highly critical of the FDA and made a number of recommendations (Pilot and Waldmann, 1998). The mid-1990s also saw the reinventing government initiatives (RIGO) chaired by Vice President AL Gore. Under RIGO, the FDA sought to identify and implement administrative reform. The RIGO report issued was entitled *Reinventing Regulation of Drugs and Medical Devices*. The 104th Congress started hearings on FDA reform again in the winter of 1995. Two bills were introduced that provided the essential outline of what would become FDAMA. Senator Nancy Kassebaum (R-KS), chair of the Senate Committee on Labor and Human Resources, introduced S-1477. The second was H.R.3201, introduced by Rep. Joe Barton (R-TX). Other bills were introduced by Senator Paul Wellstone (D-MN) and Rep. Ron Weyden (D-OR), which focused more on medical devices but sill paved the way for bipartisan support of FDA reform (Pilot and Waldmann, 1998). Eventually, the 105th Congress passed the FDAMA, which was signed into law by President Clinton in November 1997. The various sections of FDAMA are listed in Table 2.2. By any measure it was a very broad and complex, if not overly deep, piece of legislation. In 1998, Marwick (1998) observed, "a measure of the extent of the task is that implementation of the Act will require 42 new regulations, … 23 new guidance notices, and 45 reports and other tasks." The FDA has identified these various tasks, regulations, and guidances necessary for the implementation of FDAMA. (FDA's FDAMA Implementation Chart is available at http://www.fda.gov/RegulatoryInformation/egislation/SignificantAmendmentstotheFDCAct/FDAMA/FDAMAImplementationChart/default.htm, and the reader is urged to explore this site.) There is an FDAMA icon on the FDA home page, and both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) have issued various guidance documents. Some of the more interesting sections of the Act that may be of interest to toxicologists include the following:

- Two successive renewals of PDUFA for another 5 years.
- Fast track for breakthrough products.
- Changes in the fashion biologicals are regulated (elimination of the Establishment and Product licenses, both replaced with a Biologics License Application (BLA)).
- Changes in the fashion antibiotics are developed and regulated.
- Incentives for the development of pediatric claims.
- Companies will be permitted to disseminate information about approved uses for their products.
- FDAMA requires that the FDA establish a clinical trials database for drugs used to treat serious and life-threatening diseases, other than AIDS and cancers (databases for these diseases had already been established).

The full impact of FDAMA in the pharmaceutical industry in general and on toxicology within this industry in particular remains to be established.

This is a debate that has continued to the present and has been highlighted by demands for anti-HIV chemotherapeutic agents.

While it is not possible to review the history of regulations worldwide, it is possible to point out some differences. We will call attention to specific differences where appropriate throughout the remainder of the text.

The strength of the US regulatory system was emphasized at the BIO-Europe 1993 Conference. David Holtzman stated: "the main subject of the conference was regulation, and the U.S. was perceived to have the superior regulatory agency. It may be more difficult to satisfy but it is more predictable and scientifically based" (Holtzman, 1993). This predictability has not stultified growth in the biotechnology industry in the United States and has, in fact, made the United States a more inciting target for investment than Europe. It is also a system that, while not perfect, has permitted very few unsafe products on the market.

## 2.3 FDAMA SUMMARY: CONSEQUENCES AND OTHER REGULATIONS

In summary, federal regulation of the safety of drugs has had three major objectives:

1. Requiring testing to establish safety and efficacy
2. Establishing guidelines as to which tests are required and how they are designed
3. Promulgating requirements of data recording and reporting

The first of these objectives was served by the 1906 Act, which required that agents be labeled appropriately. This was amended in 1938, in response to the tragedies associated with elixir of sulfanilamide and Lash Lure, to require that drugs and marketed formulations of drugs be shown to be safe when used as intended. In the aftermath of the thalidomide tragedy, the 1962 Kefauver–Harris Amendment significantly tightened requirements for preclinical testing

**TABLE 2.2 Summary of the Contents of the 1997 Food and Drug Administration Modernization Act**

| Title/Subtitle | Section |
|---|---|
| I. Improving regulatory drugs | |
| A. Fees relating to drugs | 101. Findings<br>102. Definitions<br>103. Authority to assess and use drug fees<br>104. Annual reports<br>105. Savings<br>106. Effective date<br>107. Termination of effectiveness |
| B. Other improvements | 111. Pediatric studies of drugs<br>112. Expanding study and approval of fast-track drugs<br>113. Information program on trials for serious disease<br>114. Healthcare economic information<br>115. Manufacturing changes for drugs<br>116. Streamlining clinical research for drugs<br>118. Data requirements for drugs and biologics<br>119. Content and review of applications<br>120. Scientific advisory panels<br>121. Positron emission tomography<br>122. Requirements for radiopharmaceuticals<br>123. Modernization of regulation<br>124. Pilot- and small-scale manufacture<br>125. Insulin and antibiotics<br>126. Elimination of certain labeling requirements<br>127. Application of federal law to pharmacy compounding<br>128. Reauthorization of clinical pharmacology program<br>129. Regulation of sunscreen products<br>130. Report of postmarketing approval studies<br>131. Notification of discontinuance of a lifesaving product |
| II. Improving regulation of devices | 201. Investigational device exemptions<br>202. Special review for certain devices<br>203. Expanding humanitarian use of devices<br>204. Device standards<br>205. Collaborative determinations of device data requirements<br>206. Premarket notification<br>207. Evaluation of automatic class III designation<br>208. Classification panels<br>209. Certainty of review time frames<br>210. Accreditation of person for review of premarket notification reports<br>211. Device tracking<br>212. Postmarket notification<br>213. Reports<br>214. Practice of medicine<br>215. Noninvasive blood glucose meter<br>216. Data relating to premarket approval: product development protocol<br>217. Number of required clinical investigations for approval |
| III. Improving regulation of food | 301. Flexibility for regarding claims<br>302. Petitions for claims<br>303. Health claims for food products<br>304. Nutrient content claims<br>305. Referral statements<br>306. Disclosure of radiation<br>307. Irradiation petition<br>308. Glass and ceramic ware<br>309. Food contact substance |

**TABLE 2.2 (Continued)**

| Title/Subtitle | Section |
|---|---|
| IV. General provisions | 401. Dissemination of information new uses<br>402. Expanded access of investigational therapies and diagnostics<br>403. Approval of supplemental applications for approved products<br>404. Dispute resolution<br>405. Informal agency statements<br>406. FDA mission and annual report<br>407. Information system<br>408. Education and training<br>409. Centers for education and research on therapeutics<br>410. Mutual recognition of agreements and global harmonization<br>411. Environmental impact review<br>412. National uniformity for nonprescription drugs and cosmetics<br>413. FDA study of mercury in drugs and foods<br>414. Interagency collaboration<br>415. Contracts for expert review<br>416. Product classification<br>417. Registration of foreign establishments<br>418. Clarification of seizure authority<br>419. Interstate commerce<br>420. Safety report disclaimers<br>421. Labeling and advertising compliance with statutory requirements<br>422. Rule of construction |
| V. Effective date | 501. Effective date |

(the INDA) and premarket approval (the NDA) of new drugs. Regulations pertaining to INDAs and NDAs have been modified (most recently in 1988) but essentially remain the backbone of regulations of the toxicity evaluation of new human pharmaceutical agents.

The Good Laboratories Practice (GLP) Act, which specifies standards for study planning, personnel training, data recording, and reporting, came out in 1978 in response to perceived shoddy practices of the operations of laboratories involved in the conduct of preclinical safety studies. It was revised in 1985 and is discussed elsewhere in this book.

The final major regulatory initiative on preclinical evaluation for drug safety arose out of the AIDS crisis. To that point, the process of drug review and approval had very generally been perceived as slowing down, the FDA pursuing a conservative approach to requiring proof of safety and efficacy before allowing new drugs to become generally available. In response to AIDS, in 1988 the Expedited Delivery of Drugs for Life-Threatening Diseases Act established a basis for less rigorous standards (and more rapid drug development) in some limited cases.

In the United Kingdom, the Committee on Safety of Medicines (reporting to the minister of Health) regulates drug safety and development under the Medicines Act of 1968 (which has replaced the Therapeutic Substances Act of 1925). Details on differences in drug safety regulations in the international marketplace can be found in Alder and Zbinden (1988), but key points are presented in this chapter.

## 2.4 OVERVIEW OF US REGULATIONS

### 2.4.1 Regulations: General Considerations

The US federal regulations governing the testing, manufacture, and sale of pharmaceutical agents and medical devices are covered in Chapter 1, Title 21 of the Code of Federal Regulations (21 CFR). These comprise nine $6'' \times 8''$ (double-sided) volumes which stack $8''$ high. This title also covers foods, veterinary products, and cosmetics. As these topics will be discussed elsewhere in this book, in this chapter we will briefly review those parts of 21 CFR that are applicable to human health products and medicinal devices.

Of most interest to a toxicologist working in the pharmaceutical arena would be Chapter 1, Subchapter A (Parts 1–78), which cover general provisions, organization, etc. The GLPs are codified in 21 CFR 58.

General regulations that apply to drugs are in Subchapter C (Parts 200–299). This covers topics such as labeling, advertising, commercial registration, manufacture, and distribution. Of most interest to a toxicologist would be a section on labeling (Part 201, Subparts A–G, which covers Sections 201.1 through 201.317 of the regulations) as much of the toxicological research on a human prescription drug goes toward supporting a label claim. For example, specific requirements on content and format of labeling for human prescription drugs are covered in Section 201.57. Directions for what should be included under the "Precautions" section of a label are listed in 201.57(f). This includes 201.57(f)(6),

which covers categorization of pregnancy risk, and the reliance upon animal reproduction studies in making these categorizations is made quite clear. For example, a drug is given a pregnancy category B if "animal reproduction studies have failed to demonstrate a risk to the fetus." The point here is not to give the impression that the law is most concerned with pregnancy risk. Rather, we wish to emphasize that much basic toxicological information must be summarized on the drug label (or package insert). This section of the law is quite detailed as to what information is to be presented as well as the format of presentation. Toxicologists working in the pharmaceutical arena should be familiar with this section of the CFR.

### 2.4.2 Regulations: Human Pharmaceuticals

The regulations specifically applicable to human drugs are covered in Subchapter D, Parts 300–399. The definition of a new drug is covered in Part 310(g):

> A new drug substance means any substance that when used in the manufacture, processing or packaging of a drug causes that drug to be a new drug but does not include intermediates used in the synthesis of such substances.

The regulation then goes on to discuss "newness with regard to new formulations, indications, or in combinations." For toxicologists, the meat of the regulations can be found in Section 312 (INDA) and Section 314 (applications for approval to market a new drug or antibiotic drug or NDA). The major focus for a toxicologist working in the pharmaceutical industry is on preparing the correct toxicology "packages" to be included to "support" these two types of applications. (The exact nature of these packages will be covered in the following.)

In a nutshell, the law requires solid scientific evidence of safety and efficacy before a new drug will be permitted into clinical trials or (later) onto the market. The INDA (covered in 21CFR 310) is for permission to proceed with clinical trials on human subjects. Once clinical trials have been completed, the manufacturer or "sponsor" can then proceed to file an NDA (covered in 21 CFR 314) for permission to market the new drug.

As stated in 321.21, "A sponsor shall submit an IND if the sponsor intends to conduct a clinical investigation with a new drug… [and] shall not begin a clinical investigation until… an IND… is in effect." Similar procedures are in place in other major countries. In the United Kingdom, for example, a Clinical Trials Certificate (CTC) must be filed or a clinical trial exemption (CTX) obtained before clinical trials may proceed. Clinical trials are divided into three phases, as described in 312.21. Phase I trials are initial introductions into healthy volunteers primarily for the purposes of establishing tolerance (side effects), bioavailability, and metabolism. Phase II clinical trials are "controlled studies… to evaluate effectiveness of the drug for a particular indication or disease." The secondary objective is to determine common short-term side effects; hence the subjects are closely monitored. Phase III studies are expanded clinical trials. It is during this phase that definitive, large-scale, double-blind studies are performed.

The toxicologist's main responsibilities in the IND process are to design, conduct, and interpret appropriate toxicology studies (or "packages") to support the initial IND and then design the appropriate studies necessary to support each additional phase of investigation. Exactly what may constitute appropriate studies are covered elsewhere in this chapter. The toxicologist's second responsibility is to prepare the toxicology summaries for the (clinical) investigator's brochure (described in 312.23(a)(8)(ii)). This is an integrated summary of the toxicological effects of the drug in animals and *in vitro*. The FDA has prepared numerous guidance documents covering the content and format of INDs. It is of interest that in the Guidance for Industry (CDER and CBER, 1995), an in-depth description of the expected contents of the pharmacology and toxicology sections was presented. The document contains the following self-explanatory passage:

> Therefore, if final, fully quality-assured individual study reports are not available at the time of IND submission, an integrated summary report of toxicological findings based on the unaudited draft toxicologic reports of the completed animal studies may be submitted.

If audited draft but not yet finalized reports are used in an initial IND, the finalized report must be submitted within 120 days of the start of the clinical trial. The sponsor must also prepare a document identifying any differences between the preliminary and final reports and the impact (if any) on interpretation.

Thus, while the submission of fully audited reports is preferable, the agency does allow for the use of incomplete reports.

Once an IND or CTC/CTX is opened, the toxicologists may have several additional responsibilities: First, to design, conduct, and report the additional tests necessary to support a new clinical protocol or an amendment to the current clinical protocol (Section 312.20). Secondly, to bring to the sponsor's attention any finding in an ongoing toxicology study in animals "suggesting a significant risk to human subjects, including any finding of mutagenicity, teratogenicity or carcinogenicity," as described in 21 CFR 312.32. The sponsor has a legal obligation to report such findings within 10 working days. Third, to prepare a "list of the preclinical studies … completed or in progress during the past year" and a summary of the major preclinical findings. The sponsor is required (under Section 312.23) to file an annual report

**TABLE 2.3 Composition of Standard Investigational New Drug Application (Traditional Format)**

1. IND cover sheets (Form FDA-1571)
2. Table of contents
3. Introductory statement
4. General (clinical) investigation plan
5. (Clinical) investigators brochure
6. (Proposed) clinical protocol(s)
7. Chemistry, manufacturing, and control information (CMC)
8. Pharmacology and toxicology information
   (includes metabolism and pharmacokinetic assessments done in animals)
9. Previous human experience with the investigational drug
10. Additional information
11. Other relevant information

(within 60 days of the IND anniversary date) describing the progress of the investigation. INDs are never "approved" in the strict sense of the word. Once filed, an IND can be opened 30 days after submission, unless the FDA informs the sponsor otherwise. Complete and thorough reports on all pivotal toxicological studies must be provided with the application. The structure of an IND is outlined in Table 2.3.

If the clinical trials conducted under an IND are successful in demonstrating safety and effectiveness (often established at a pre-NDA meeting, described in 21 CFR 312.47(b)(2)), the sponsor can then submit an NDA. Unlike an IND, the NDA must be specifically approved by the agency. The toxicologist's responsibility in the NDA/Marketing Authorization Application (MAA) process is to prepare an integrated summary of all the toxicology and/or safety studies performed and be in a position to present and review the toxicology findings to the FDA or its advisory bodies. The approval process can be exhausting, including many meetings, hearings, appeals, etc. The ground rules for all of these are described in Part A of the law. For example, all NDAs are reviewed by an "independent" (persons not connected with either the sponsor or the agency) scientific advisory panel which reviews the findings and makes recommendations as to approval. MAAs must be reviewed by and reported on by an expert recognized by the cognizant regulatory authority. Final statutory approval in the United States lies with the Commissioner of the FDA. It is hoped that few additional studies will be requested during the NDA review and approval process. When an NDA is approved, the agency will send the sponsor an approval letter and will issue a Summary Basis of Approval (SBA)(312.30), which is designed and intended to provide a public record on the agency's reasoning for approving the NDA while not revealing any proprietary information. The SBA can be obtained through Freedom of Information and can provide insights into the precedents for which types of toxicology studies are used to support specific types of claims.

### 2.4.3 Regulations: Environmental Impact

Environmental impact statements, while once important only for animal drugs, must now accompany all MDAs. This assessment must also be included in the Drug Master File (DMF). The procedures, formats, and requirements are described in 21 CFR 2531. This requirement has grown in response to the National Environmental Policy Act, the heart of which required that federal agencies evaluate every major action that could affect the quality of the environment. In the INDs, this statement can be a relatively short section claiming that relatively small amounts will post little risk to the environment. The EEC has similar requirements for drug entities in Europe, though data requirements are more strenuous. With NDAs, this statement must be more substantial, detailing any manufacturing and/or distribution process that may result in release into the environment. Environmental fate (e.g., photohydrolysis) and toxicity (e.g., fish, daphnia, and algae) studies will be required. While not mammalian toxicology in the tradition of pharmaceutical testing, preparing an environmental impact statement will clearly require toxicological input. The FDA has published a technical bulletin covering the tests it may require (FDA, 1987).

### 2.4.4 Regulations: Antibiotics

The NDA law (safety and effectiveness) applies to all drugs, but antibiotic drugs were treated differently until the passage of FDAMA in 1997. Antibiotic drugs had been treated differently by the FDA since the development of penicillin revolutionized medicine during World War II. The laws applicable to antibiotic drugs were covered in 21 CFR 430 and 431. Antibiotics such as penicillin or doxorubicin are drugs derived (in whole or in part) from natural sources (such as molds or plants) which have cytotoxic or cytostatic properties. They were treated differently from other drugs as the applicable laws required a batch-to-batch certification process. Originally passed into law in 1945 specifically for penicillin, this certification process was expanded by the 1962 amendment (under Section 507 of the FDCA) to require certification of all antibiotic drugs, meaning that the FDA would assay each lot of antibiotic for purity, potency, and safety. The actual regulations were covered in 21 CFR Subchapter D, Parts 430–460 (over 600 pages), which describes the standards and methods used for certification for all approved antibiotics. Section 507 was repealed by FDAMA (Section 125). As a result of the repeal of Sections 507, the FDA is no longer required to publish antibiotic monographs. In addition, the testing, filing, and reviewing of antibiotic applications are now handled under Section 505 of the Act like any other new therapeutic agent. The FDA has published a guidance document to which the reader is referred for more details (CDER, 1998).

### 2.4.5 Regulations: Biologics

Biological products are covered in Subchapter F, Parts 600–680. As described in 21 CFR 600.3(h), "biological product means any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man." In other words, these are vaccines and other protein products derived from animal sources. Clearly the toxicological concerns with such products are vastly different than those involved with low molecular weight synthetic molecules. There is little rational basis, for example, for conducting a 1-year repeated-dose toxicity study with a vaccine or a human blood product. The FDA definition for safety with regard to these products is found in 21 CFR 603.1(p): "Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered." Such safety consideration has more to do with purity, sterility, and adherence to good manufacturing standards than with the toxicity of the therapeutic molecule itself. The testing required to show safety is stated in licensing procedures 21 CFR 601.25(d)(1): "Proof of safety shall consist of adequate test methods reasonably applicable to show the biological product is safe under the prescribed conditions." Once a license is granted, each batch or lot of biological product must be tested for safety, and the methods of doing so are written into the law. A general test for safety (i.e., required in addition to other safety tests) is prescribed using guinea pigs as described in 610.11. Additional tests are often applied to specific products. For example, 21 CFR 630.35 describes the safety tests required for measles vaccines, which includes tests in mice and *in vitro* assays with tissue culture. Many new therapeutic entities produced by biotechnology are seeking approval as biologics with the results being FDA approval of a Product License Application (PLA). Table 2.4 presents general guidance for the basis of deciding if an individual entity falls under CDER or CBER authority for review.

The International Conference on Harmonization (ICH) has published its document S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. The FDA (both CDER and CBER jointly) has published the document as a Guidance for Industry (FDA, 1997).

A current list of regulatory documents (including the most recent points to consider (PTCs)) can be found on the FDA website by accessing the FDA home page at www.fda.gov, scrolling down and finding the "Regulatory Information" tab with applicable links near the bottom left. The Regulatory Information site can also be directly accessed using the following web address: http://www.fda.gov/RegulatoryInformation/default.htm

### 2.4.6 Regulations versus Law

A note of caution must be inserted here. The law (document passed by Congress) and the regulations (documents written by regulatory authorities to enforce laws) are separate documents. Sections in the law do not necessarily have numerical correspondence with those of the regulations. For example, the regulations on the NDA process are described in 21 CFR 312, but the law describing the requirement for an NDA process is in Section 505 of the FDCA. Because regulations rather than laws themselves have a greater impact on toxicological practice, greater emphasis is placed on regulation in this chapter. For a complete review of FDA law, the reader is referred to the monograph by Food and Drug Law Institute in 1984.

Laws authorize the activities and responsibilities of the various federal agencies. All proposed laws before the US Congress are referred to committees for review and approval. The committees responsible for FDA oversight are summarized in Table 2.5. This table also highlights that authorizations and appropriations (the funding necessary to execute authorizations) are handled by different committees.

**TABLE 2.4 Product Class Review Responsibilities**

| |
|---|
| *Center for Drug Evaluation and Research* |
| Natural products purified from plant or mineral sources |
| Products produced from solid tissue sources (excluding procoagulants, venoms, blood products, etc.) |
| Antibiotics, regardless of method of manufacture |
| Certain substances produced by fermentation |
| Disaccharidase inhibitors |
| HMG-CoA inhibitors |
| Synthetic chemicals |
| Traditional chemical synthesis |
| Synthesized mononuclear or polynuclear products including antisense chemicals |
| Hormone products |
| *Center for Biologics Evaluation and Research* |
| Vaccines, regardless of manufacturing method |
| *In vivo* diagnostic allergenic products |
| Human blood products |
| Protein, peptide, and/or carbohydrate products produced by cell culture (other than antibiotics and hormones) |
| Immunoglobulin products |
| Products containing intact cells or microorganisms |
| Proteins secreted into fluids by transgenic animals |
| Animal venoms |
| Synthetic allergens |
| Blood banking and infusion adjuncts |

## 2.5 ORGANIZATIONS REGULATING DRUG AND DEVICE SAFETY IN THE UNITED STATES

The agency formally charged with overseeing the safety of drugs in the United States is the FDA. The FDA is headed by a commissioner who reports to the Secretary of the Department of Health and Human Services (DHHS) and has a tremendous range of responsibilities. Drugs are

**TABLE 2.5 Congressional Committees Responsible for FDA Oversight**

| | |
|---|---|
| *Authorization* | |
| Senate | All public health service agencies are under the jurisdiction of the Labor and Human Resources Committee |
| House | Most public health agencies are under the jurisdiction of the Health and the Environmental Subcommittee of the House Energy and Commerce Committee |
| *Appropriation* | |
| Senate | Unlike most other public health agencies, the FDA is under the jurisdiction of the Agriculture, Rural Development, and Related Agencies Subcommittee of the Senate Appropriations Committee |
| House | Under the jurisdiction of the Agriculture, Rural Development, and Related Agencies Subcommittee of the House Appropriations Committee |

overseen primarily by the CDER (though some therapeutic or healthcare entities are considered biologics and are overseen by the corresponding CBER). Figure 2.1 presents the organization of CDER, and that of CBER is shown in Figure 2.2.

Most of the regulatory interactions of toxicologists take place with these two offices of Drug Evaluation, which have under them a set of groups focused on areas of therapeutic claim (cardiorenal, neuropharmacological, gastrointestinal and coagulation, oncology and pulmonary, metabolism and endocrine, anti-infective and antiviral). Within each of these are chemists, pharmacologists/toxicologists, statisticians, and clinicians. When an INDA is submitted to the offices of Drug Evaluation, it is assigned to one of the therapeutic groups based on its area of therapeutic claim. Generally, it will remain with that group throughout its regulatory approval "life." INDs, when allowed, grant investigators the ability to go forward into clinical (human) trials with their drug candidate in a predefined manner, advancing through various steps of evaluation in human (and in additional preclinical or animal studies) until an NDA can be supported, developed, and submitted. Likewise for biological products, the PLA or other applications (INDA, IND) are handled by the offices of Biological Products Review within the CBER.

For drugs, there is at least one nongovernmental body which must review and approve various aspects—the USP (established in 1820)—which maintains (and revises) the compendia of the same name, as well as the National Formulary which sets drug composition standards (Ember, 2001). This volume sets forth standards for purity of products in which residues may be present and tests for determining various characteristics of drugs, devices, and biologics. The USP also contains significant "guidance" for the evaluation process (USP, 2015).

## 2.6 PROCESS OF PHARMACEUTICAL PRODUCT DEVELOPMENT AND APPROVAL

Except for a very few special cases (treatments for life-threatening diseases such as cancer or AIDS), the safety assessment of new drugs is mandated by regulations which seemingly proceed in a rather fixed manner. The IND is filed to support (or enable) clinical testing and development of the drug. An initial set of studies (typically, studies of appropriate length by the route intended for humans are performed in both a rodent (typically rat) and a nonrodent (usually a dog or a primate)) are required to support phase I clinical testing. Such phase I testing is intended to evaluate the safety ("tolerance" in clinical subjects), pharmacokinetics, and general biological effects of a new drug and is conducted in normal volunteers (almost always males).

Successful completion of phase I testing allows, with the approval of the FDA, progression into phase II clinical testing. Here, selected patients are enrolled to evaluate therapeutic efficacy, dose ranging, and more details about the pharmacokinetics and metabolism. Longer-term systemic toxicity studies must be in conformity with the guidelines that are presented in the next section. Once a sufficient understanding of the actions, therapeutic dose–response, and potential risk-to-benefit ratio of a drug is in hand (once again, with FDA approval), trials move into phase III testing.

Phase III tests are large, long, and expensive. They are conducted using large samples of selected patients and are intended to produce proof of safety and efficacy of a drug. Two studies providing statistically significant proof of the claimed therapeutic benefit must be provided. All resulting data from preclinical and clinical animal studies are organized in a specified format in the form of an NDA, which is then submitted to the FDA.

By the time phase III testing is completed, some additional preclinical safety tests must also generally be in hand. These include the three separate reproductive and developmental toxicity studies (segments I and III in the rat and segment II in the rat and rabbit) and carcinogenicity studies in both rats and mice (unless the period of therapeutic usage is intended to be very short). Some assessment of genetic toxicity will also be expected.

The ultimate product of the pharmaceutical toxicologist will thus generally be the toxicology summaries of the IND and NDA (or PLA). For medical devices, the equivalents are the Investigational Device Exemption (IDE) and Product Development Notification (PDN). Data required to support each of these documents is specified in a series of guidelines, as will be discussed in the following.

Acceptance of these applications is contingent not only upon adherence to guidelines and good science but also adherence to GLPs.

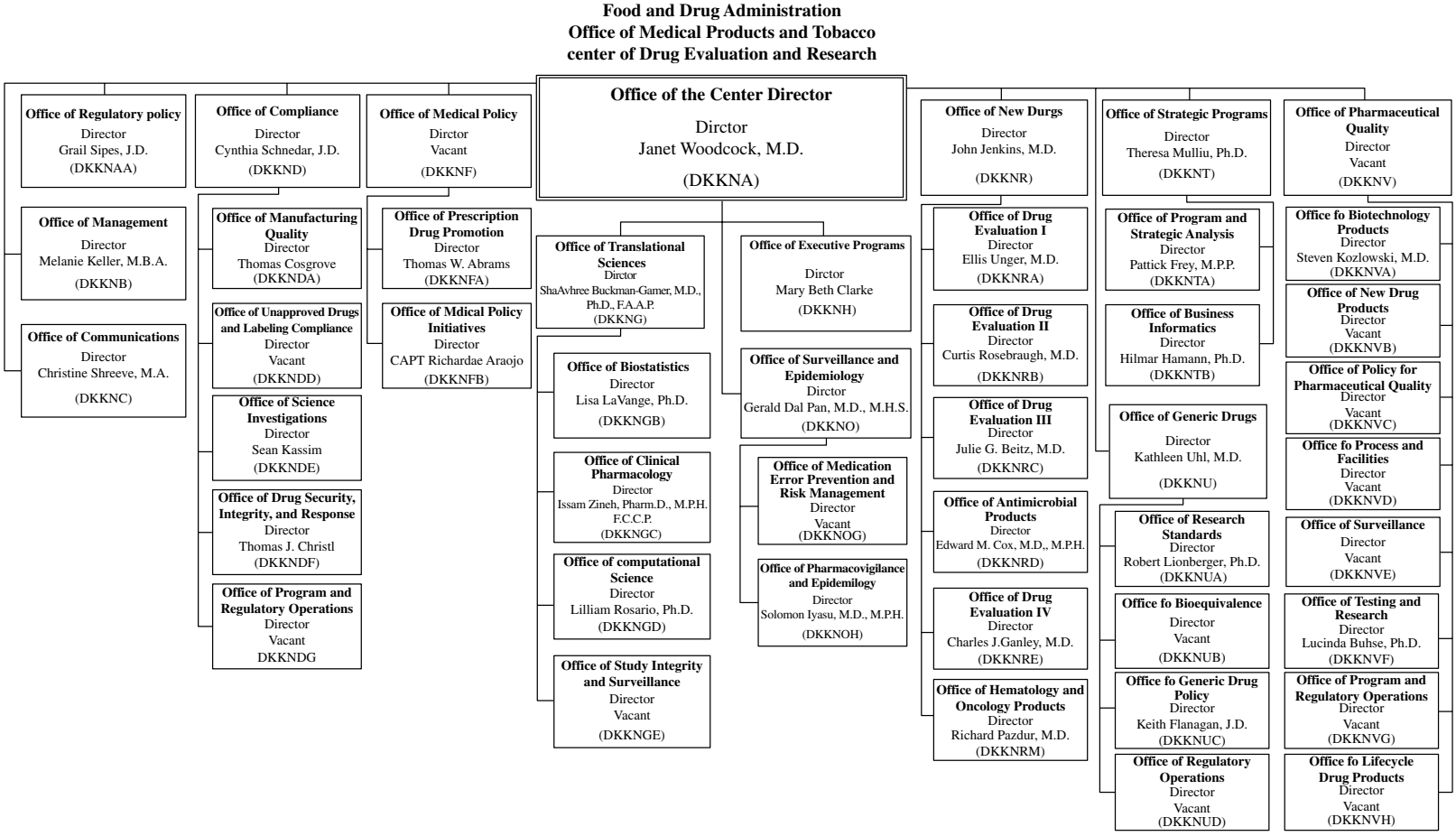



**FIGURE 2.1** Center for Drug Evaluation and Research (CDER). *Source*: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM439876.pdf

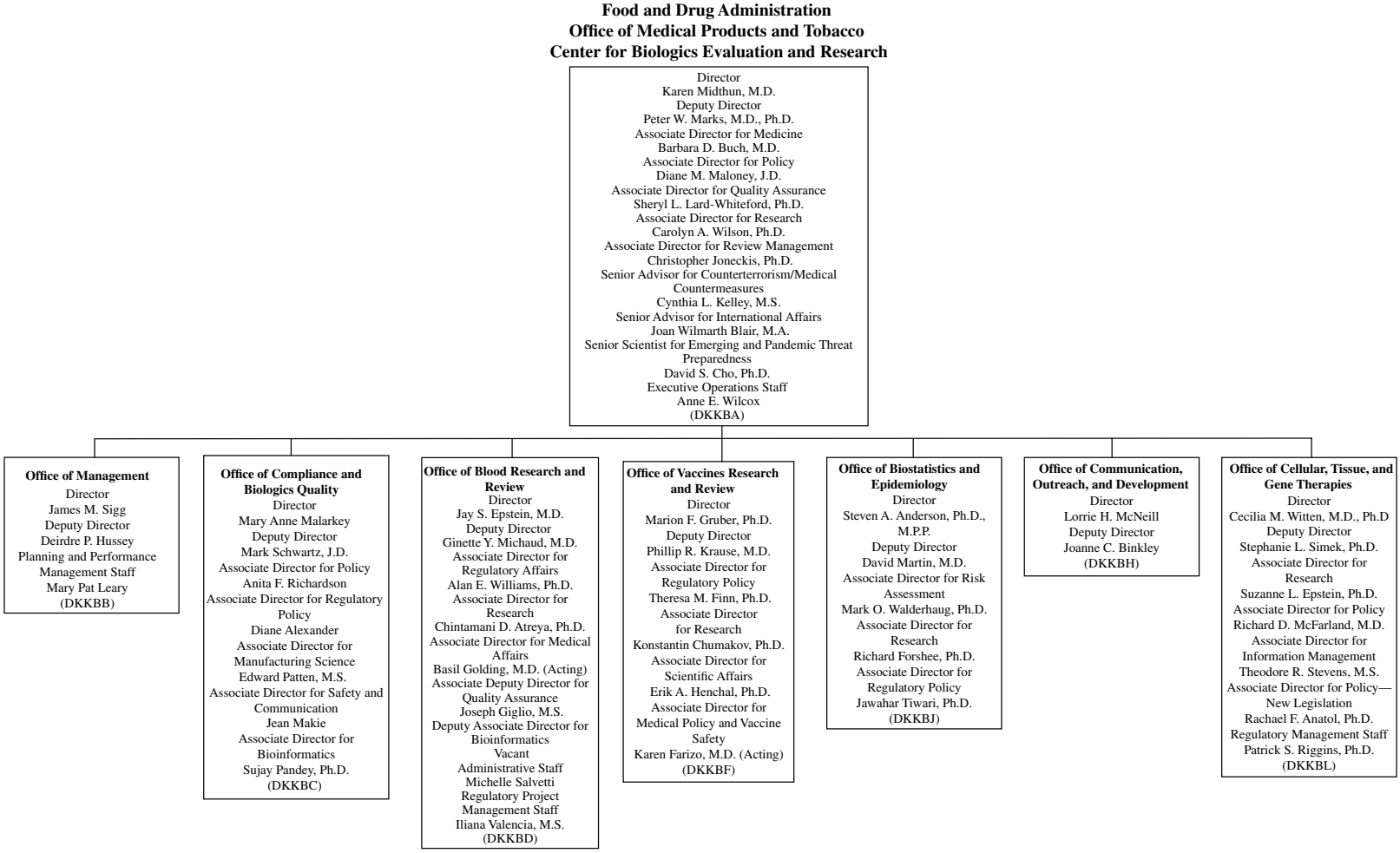



**FIGURE 2.2** Center for Biologics Evaluation and Research (CBER). *Source*: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm347874.htm

## 2.7 TESTING GUIDELINES

### 2.7.1 Toxicity Testing: Traditional Pharmaceuticals

Although the 1938 Act required safety assessment studies, no consistent guidelines were available. Guidelines were first proposed in 1949 and published in the *Food, Drug, and Cosmetic Law Journal* that year (Burns, 1983). Following several revisions, these guidelines were issued as the Appraisal Handbook in 1959. While never formally called a guideline, it set the standard for preclinical toxicity test design for several years. The current basic guidelines for testing required for safety assessment in support of the phases of clinical development of drugs were first outlined by Goldenthal (1968) and later incorporated into a 1971 FDA publication entitled *FDA Introduction to Total Drug Quality*.

All general case pharmaceuticals need to address four major aspects of toxicology before going into humans. These are systemic toxicity, potential genetic toxicity, safety pharmacology, and (if any route of administration other than oral) local tissue tolerance issues.

### 2.7.2 General or Systematic Toxicity Assessment

Table 2.6 presents an overview of the current FDA toxicity testing guidelines for human drugs. Table 2.7 presents the parallel ICH guidance (ICH, 2009) which now largely supplants the FDA guidelines. They are misleading in their apparent simplicity, however. First, each of the systemic toxicity studies in these guidelines must be designed and executed in a satisfactory manner. Sufficient animals must be used to have confidence in finding and characterizing any adverse drug actions that may be present. In practice, as the duration of the study increases, small doses are administered, and larger numbers of animals must be employed per group. These two features—dosage level and group size—are critical to study designs. Table 2.8 presents general guidance on the number of animals to be used in systemic studies. These and other technical considerations for the safety assessment of pharmaceuticals are present in detail in this book.

The protocols discussed thus far have focused on general or systemic toxicity assessment. The agency and, indeed, the lay public have a special set of concerns with reproductive toxicity, fetal/embryo toxicity, and developmental toxicity (also called *teratogenicity*). Collectively, these concerns often go by the acronyms *DART* (developmental and reproductive toxicity) or *RTF* (reproduction, teratogenicity, fertility). Segment II studies are more designed to detect developmental toxicity. Only pregnant females are dosed during critical period of organogenesis. Generally, the first protocol DART test (exclusive of range-finding studies) is a segment I study of rats in fertility and general reproductive performance. This is generally done while the drug is in phase II clinical trials. Alternatively, many companies are now performing the segment II teratology study in rats before the segment I study because the former is less time and resource intensive. One or both should be completed before including women of childbearing potential in clinical trials. The FDA requires teratogenicity testing in two species—a rodent (rat or mouse) and the rabbit. Use of the rabbit was instituted as a result of the finding that thalidomide was a positive teratogen in the rabbit but not in the rat. On occasion, when a test article is not compatible with the rabbit, teratogenicity data in the mouse may be substituted. There are also some specific classes of therapeutics (e.g., quinolone antibiotics) where segment II studies in primates are effectively required prior to product approval. Both should be completed before entering phase III clinical trials. The most complicated of the DART protocols—segment III—is generally commenced during phase III trials and should be part of the NDA. There are differences in the different national guidelines (as discussed later with international considerations) regarding the conduct of these studies. The large multinational drug companies try to design their protocols to be in compliance with as many guidelines as possible to avoid duplication of testing while allowing the broadest possible approval and marketing of therapeutics.

### 2.7.3 Genetic Toxicity Assessment

Genetic toxicity testing generally focuses on the potential of a new drug to cause mutations (in single-cell systems) or other forms of genetic damage. The tests, generally short in duration, often rely on *in vitro* systems and generally have a single end point of effect (point mutations, chromosomal damage, etc.). For a complete review of protocols, technology, etc., the reader is referred to Brusick (1987). It is of interest that the FDA had no standard or statutory requirement for genetic toxicity testing but generally expects to see at least some such tests performed and will ask for them if the issue is not addressed. If one performs such a study, any data collected, of course, must be sent to the agency as part of any INDA, PLA, or NDA. These studies have yet to gain favor with the FDA (or other national regulatory agencies) as substitutes for *in vivo* carcinogenicity testing. However, even with completed negative carcinogenicity tests, at least some genetic toxicity assays are generally required. Generally, pharmaceuticals in the United States are evaluated for mutagenic potential (e.g., the Ames assay) or for chromosomal damage (e.g., the *in vivo* mouse micronucleus test). In general, in the United States, pharmaceutical companies apply genetic toxicity testing in the following fashion:

- *As a screen* An agent that is positive in one or more genetic toxicity tests may be more likely than one that is negative to be carcinogenic and, therefore, may not warrant further development.
- *As an adjunct* An agent that is negative in carcinogenicity testing in two species and also negative in a genetic toxicity battery is more likely than not to be noncarcinogenic in human beings.

**TABLE 2.6 Synopsis of General Guidelines for Animal Toxicity Studies for Drugs**

| Category | Duration of Human Administration | Clinical Phase | Subacute or Chronic Toxicity | Special Studies |
|---|---|---|---|---|
| Oral or parenteral | Several days | I, II, III, NDA | Two species; 2 weeks | For parentally administered drugs |
| | Up to 2 weeks | I | Two species; 4 weeks | |
| | | II | Two species; up to 4 weeks | |
| | | III, NDA | Two species; up to 3 months | Compatibility with blood where applicable |
| | Up to 3 months | I, II | Two species; 4 weeks | |
| | | III | Two species; 3 months | |
| | | NDA | Two species; up to 6 months | |
| | 6 months to unlimited | I, II | Two species; 3 months | |
| | | III | Two species; 6 months or longer | |
| | | NDA | Two species; 9 months (nonrodent) and 12 months (rodent) | |
| | | | +2 rodent species for CA; 18 months (mouse); 24 months (rat). Mouse may be replaced with an allowable transgenic mouse study | |
| Inhalation (general anesthetics) | | I, II, III, NDA | Four species; 5 days (3 h $day^{-1}$) | |
| Dermal | Single application | I | One species; single 24 h exposure followed by 2-week observation | Sensitization |
| | Single or short-term application | II | One species; 20-day repeated exposure (intact and abraded skin) | |
| | Short-term application | III | As aforementioned | |
| | Unlimited application | NDA | As aforementioned, but intact skin study extended up to 6 months | |
| Ophthalmic | Single application | I | | Eye irritation tests with graded doses |
| | Multiple application | I, II, III | One species; 3-week daily applications, as in clinical use | |
| | | NDA | One species; duration commensurate with period of drug administration | |
| Vaginal or rectal | Single application | I | | Local and systematic toxicity after vaginal or rectal application in two species |
| | Multiple application | I, II, III, NDA | Two species; duration and number of applications determined by proposed use | |
| Drug combinations | | I, II, III, NDA | Two species; up to 3 months | Lethality by appropriate route, compared to components run concurrently in one species |

**TABLE 2.7 Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials and Marketing[a]**

| Duration of Clinical Trials | Minimum Duration of Repeated-Dose Toxicity Studies[b] | | Duration of Clinical Trials | Minimum Duration of Repeated-Dose Toxicity Studies[c] | |
|---|---|---|---|---|---|
| | Rodents | Nonrodents | | Rodents | Nonrodents |
| Single dose | 2 weeks[d] | 2 weeks | Up to 2 weeks | 1 month | 1 month |
| Up to 2 weeks | 2 weeks[d] | 2 weeks | Up to 1 month | 3 months | 3 months |
| Up to 1 month | 1 month | 1 month | Up to 3 months | 6 months | 3 months |
| Up to 6 months | 6 months | 6 months[e] | >3 months | 6 months | Chronic[d] |
| >6 months | 6 months | Chronic[e] | | | |

[a] In Japan, if there are no phase II clinical trials of equivalent duration to the planned phase III trials, conduct of longer duration toxicity studies is recommended as given earlier.
[b] Data from 6 months of administration in nonrodents should be available before the initiation of clinical trials longer than 3 months. Alternatively, if applicable, data from a 9-month nonrodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.
[c] The table also reflects the marketing recommendations in the three regions except that a chronic nonrodent study is recommended for clinical use >1 month.
[d] In the United States, as an alternative to 2-week studies, single-dose toxicity studies with extended examinations can support single-dose human trials (4).
[e] To support phase I and II trials in the EU and phase I, II, and III trials in the United States and Japan.

**TABLE 2.8 Numbers of Animals per Dosage Group in Systemic Toxicity Studies (OECD Guidances)**

| Study Duration (per Sex) | Rodents (per Sex) | Nonrodents |
|---|---|---|
| 2–4 weeks | 5 | 3 |
| 13 weeks | 20[a] | 6 |
| 26 weeks | 30 | 8 |
| Chronic | 50 | 10 |
| Carcinogenicity | 60[b] | Applies only to contraceptives |
| Bioassays | | Applies only to contraceptives |

[a] Starting with 13-week studies, one should consider adding animals (particularly to the high dose) to allow evaluation of reversal of effects.
[b] In recent years there have been decreasing levels of survival in rats on 2-year studies. What is required is that at least 20–25 animals/sex/group survive at the end of the study. Accordingly, practice is beginning to use 70 or 75 animals per sex, per group.

- *To provide mechanistic insight* For example, if an agent is negative in a wide range of genetic toxicity screens but still produces tumors in animals, then one could hypothesize that an epigenetic mechanism was involved.

While not officially required, the FDA does have the authority to request, on a case-by-case basis, specific tests it feels may be necessary to address a point of concern. A genetic toxicity test could be part of such a request. In general, therefore, companies deal with genetic toxicity (after "screening") on a case-by-case basis, dictated by good science. If more than a single administration is intended, common practice is to perform the tests prior to submitting an IND.

### 2.7.4 Safety Pharmacology

Midway through 2001 ICH and the related regional regulatory authorities (such as FDA, EMA, and MHW) implemented a new set of preclinical (to be completed before initiation of human clinical trials) safety assessment requirements focused on reversible organ function alterations that could have rapid fatal effects before reversal. The general case core set of these is the freestanding GLP evaluations of cardiovascular, respiratory, pulmonary, and central nervous system (CNS) functions. There are exceptions for the "requirements" in some structural class cases. This is discussed in detail in Chapter 18 and in Gad (2012).

### 2.7.5 Local Tissue Tolerance

Not called out in ICH guidances but rather in the US and other pharmacopoeia are the requirements to assess local tissue effects of drugs as they potentially can occur at or around the site of drug application or administration. These effects include irritation, pyrogenicity, hemolysis, and others. There are specific requirements (as presented in Chapter 16) for all routes except oral.

### 2.7.6 Toxicity Testing: Biotechnology Products

As mentioned, the regulation of traditional pharmaceuticals (small molecules such as aspirin or digitalis) and biologicals (proteins such as vaccines and antitoxins derived from animal sources) has very different histories. See the discussion on biologics earlier in this chapter. Until 1972, the NIH (or its forerunning agency, the Hygienic Laboratory of the Department of the Treasury) was charged with the responsibility of administering the Virus Act of 1902. With the passage of the food and drug laws of 1906, 1938, and 1962, there was a recurring debate regarding whether these laws applied or should apply to biologicals (Pendergast, 1984). This debate was resolved when the authority for the regulation of biologics was transferred to the FDA's new Bureau of Biologics (now the CBER) in 1972. Since then, there appears to have been little difference in the matter of regulation for biologics and pharmaceuticals. The FDA essentially regulates biologics as described under the 1902 Act but then uses the rule-making authority granted under the Food and Drug Act to "fill in the gaps."

The Bureau of Biologics was once a relatively "sleepy" agency, primarily concerned with the regulation of human blood products and vaccines used for mass immunization programs. The authors of the 1902 law could hardly have foreseen the explosion in biotechnology that occurred in the 1980s. New technology created a welter of new biological products, such as recombinant DNA (rDNA)-produced proteins (e.g., tissue plasminogen activator), biological response modifiers (cytokinins and colony-stimulating factors), monoclonal antibodies, antisense oligonucleotides, and self-directed vaccines (raising an immune response to self-proteins such as gastrin for therapeutic reasons). The new products raised a variety of new questions on the appropriateness of traditional methods for evaluating drug toxicity that generated several PTC documents. For the sake of brevity, this discussion will focus on the rDNA proteins. Some of the safety issues that have been raised over the years:

- The appropriateness of testing a human-specific peptide hormone in nonhuman species
- The potential that the peptide could break down due to nonspecific metabolism, resulting in products that had no therapeutic value or even a toxic fragment
- The potential sequelae to an immune response (formation of neutralizing antibodies, provoking an autoimmune or a hypersensitivity response), pathology due to immune precipitation, etc.
- The presence of contamination with oncogenic virus DNA (depending on whether a bacterial or mammalian system was used on the synthesizing agent) or endotoxins
- The difficulty interpreting the scientific relevance of response to supraphysiological systemic doses of potent biological response modifiers

The last few intervening years have shown some of these concerns to have been more relevant than others. The "toxic peptide fragment" concern, for example, has been shown to be without merit. The presence of potentially oncogenic virus DNA and endotoxins is a quality assurance concern and is not truly a toxicological problem. Regardless of the type of synthetic pathway, all proteins must be synthesized in compliance with Good Manufacturing Practices (GMPs). Products must be as pure as possible, not only free of rDNA but also free of other types of cell debris (endotoxin). Batch-to-batch consistency with regard to molecular structure must also be demonstrated using appropriate methods (e.g., amino acid). The regulatory thinking and experience over the last 15 years has come together in the document "S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" prepared by the ICH. The FDA (both CDER and CBER jointly) has published the document as a Guidance for Industry (FDA, 1997; CDER, 1998). The document intended to provide basic guidance for the preclinical evaluation of biotechnology-derived products, including proteins and peptides, either produced by cell culture using rDNA technology, but did not cover antibiotics, allergenic extracts, heparin, vitamins, cellular drug products vaccines, or other products regulated as biologics. Items covered are summarized as follows:

- *Test-article specifications* In general, the product that is used in the definitive pharmacology and toxicology studies should be comparable to the product proposed for the initial clinical studies.
- *Animal species/model selection* Safety evaluation should include the use of relevant species, in which the test article is pharmacologically active due, for example, to the expression of the appropriate receptor molecule. These can be screened with *in vitro* receptor binding assays. Safety evaluation should normally include two appropriate species, if possible and/or feasible. The potential utility of gene knockout and/or transgenic animals in safety assessment is discussed.
- *Group size* No specific numbers are given, but it does state that a small sample size may lead to failure to observe toxic events.
- *Administration* The route and frequency should be as close as possible to that proposed for clinical use. Other routes can be used when scientifically warranted.
- *Immunogenicity* It has also been clearly demonstrated in the testing of rDNA protein products that animals will develop antibodies to foreign proteins. This response has been shown to neutralize (rapidly remove from circulation) the protein, but no pathological conditions have been shown to occur as a sequelae to the immune response. Bear in mind, however, that interleukins have powerful effects on immune response, but

these are due to their physiological activity and not due to an antigen–antibody response. The first has to do with "neutralizing antibodies;" that is, is the immune response so great that the test article is being removed from circulation as fast as it is being added? If this is the case, does long-term testing of such a chemical make sense? In many cases, it does not. The safety testing of any large molecule should include the appropriate assays for determining whether the test system has developed a neutralizing antibody response. Depending on the species, route of administration, intended therapeutic use, and development of neutralizing antibodies (which generally takes about 2 weeks), it is rare for a toxicity test on an rDNA protein to be of a duration longer than 4 weeks. However, if the course of therapy in humans is to be longer than 2 weeks, formation of neutralizing antibodies must be demonstrated or longer-term testing performed. The second antigen–antibody formation concern is that a hypersensitivity response will be elicited. Traditional preclinical safety assays are generally adequate to guard against this if they are 2 weeks or longer in duration and the relevant end points are evaluated.

- *Safety pharmacology* It is important to investigate the potential for unwanted pharmacological activity in appropriate animal models and to incorporate monitoring for these activities in toxicity studies.
- *Exposure assessment* Single- and multiple-dose pharmacokinetics, toxicokinetics, and tissue distribution studies in relevant species are useful. Proteins are not given orally, demonstrating absorption and mass balance are not typically primary considerations. Rather, this segment of the test should be designed to determine half-life (and other appropriate pharmacokinetic (PK) descriptor parameters), the plasma concentration associated with biological effects, and potential changes due to the development of neutralizing antibodies.
- *Reproductive performance and developmental toxicity studies* These will be dictated by the product, clinical indication, and intended patient population.
- *Genotoxicity studies* The S6 document states that the battery of genotoxicity studies routinely conducted for traditional pharmaceuticals are not appropriate for biotechnology-derived pharmaceuticals. In contrast to small molecules, genotoxicity testing with a battery of *in vitro* and *in vivo* techniques of protein molecules has not become common US industry practice. Such tests are not formally required by the FDA but, if performed, must be reported. They are, however, required by European and Japanese regulatory authorities. This has sparked a debate as to whether or not genotoxicity testing is necessary or appropriate for rDNA protein molecules. It is the authors' opinion that such testing is, scientifically, of little value. Firstly, large protein molecules will not easily penetrate the cell wall of bacteria or yeast, and (depending on size, charge, lipophilicity, etc.) penetration across the plasma lemma of mammalian cells will be highly variable. Secondly, if one considers the well-established mechanism(s) of genotoxicity of small molecules, it is difficult to conceive of how a protein might act in the same fashion. For example, proteins will not be metabolized to be electrophilic active intermediates that will cross-link guanine residues. In general, therefore, genotoxicity testing with rDNA proteins is wasteful of resources. It is conceivable, however, that some proteins, because of their biological mechanism of action, may stimulate the proliferation of transformed cells. For example, it is a feasible hypothesis that a colony-stimulating factor could stimulate the proliferation of leukemic cells (it should be emphasized that this is a hypothetical situation, presented here for illustrative purposes). Again, this is a question of a specific pharmacological property, and such considerations should be tested on a case-by-case basis.
- *Carcinogenicity studies* These are generally inappropriate for biotechnology-derived pharmaceuticals; however, some products may have the potential to support or induce proliferation of transformed cells—possibly leading to neoplasia. When this concern is present, further studies in relevant animal models may be needed.

These items are covered in greater detail in the S6 guidance document and in a review by Hayes and Ryffel (1997).

So, given the previous discussion, what should the toxicology testing package of a typical rDNA protein resemble? Based on the products that have successfully wended their way through the regulatory process, the following generalizations can be drawn:

- The safety tests look remarkably similar to those for traditional tests. Most have been done on three species: the rat, the dog, or the monkey. The great difference has to do with test length. It is rare for a safety test on a protein to be more than 13 weeks long.
- The dosing regimens can be quite variable and at times very technique intensive. These chemicals are almost always administered by a parenteral route of administration, normally intravenously or subcutaneously. Dosing regimens have run the range from once every 2 weeks for an antihormone "vaccine" to continuous infusion for a short-lived protein.
- As reviewed by Ryffel (1996), most side effects in man of a therapy with rDNA therapy may be predicted

by data from experimental toxicology studies, but there are exceptions. IL-6, for example, induced a sustained increase in blood platelets and acute-phase proteins, with no increase in body temperature. In human trials, however, there were increases in temperature.

- The S6 document also mentions monoclonal antibody products. Indeed, many of the considerations for rDNA products are also applicable to monoclonal antibodies (including hybridized antibodies). With monoclonal antibodies, there is the additional concern of cross-reactivity with nontarget molecules.

As mentioned, the rapid development in the biotechnology industry has created some confusion as to what arm of the FDA is responsible for such products. In October 1992, the two major reviewing groups, CBER and CDER, reached a series of agreements to explain and organize the FDA's position on products that did not easily fall into its traditional classification schemes. CDER would continue to have responsibility for traditional chemically synthesized molecules as well as those purified from mineral or plant sources (except allergenics), antibiotics, hormones (including insulin, growth hormone, etc.), most fungal or bacterial products (disaccharidase inhibitors), and most products from animal or solid human tissue sources. CBER would have responsibility for products subject to licensure (BLA), including all vaccines, human blood or blood-derived products (as well as drugs used for blood banking and transfusion), immunoglobulin products, products containing intact cells, fungi, viruses, proteins produced by cell culture or transgenic animals, and synthetic allergenic products. This situation was further simplified by the introduction of the concept of "well-characterized biologics." When introduced during the debate on FDA reform in 1996, the proposed section of S.1447 stated that "Biological products that the secretary determines to be well-characterized shall be regulated solely under the Federal Food, Drug and Cosmetic Act." Under this concept, highly purified, well-characterized therapeutic rDNA proteins would be regulated by CDER, regardless of therapeutic target (Anonymous, 1996).

## 2.8 TOXICITY/SAFETY TESTING: CELLULAR AND GENE THERAPY PRODUCTS

Human clinical trials of cellular and gene therapies involve administration to patients of materials considered investigational biological, drug, or device products. Somatic cell therapy refers to the administration to humans of autologous, allogenic, or xenogenic cells which have been manipulated or processed *ex vivo*. Gene therapy refers to the introduction into the human body of genes or cells containing genes foreign to the body for the purposes of prevention, treatment, diagnosing, or curing disease.

Sponsors of cellular or gene therapy clinical trials must file an INDA or in certain cases an IDE with the FDA before initiation of studies in humans. It is the responsibility of the CBER to review the application and determine if the submitted data and the investigational product meet applicable standards. The critical parameters of identity, purity, potency, stability, consistency, safety, and efficacy relevant to biological products are also relevant to cellular and gene therapy products.

In 1991, FDA first published "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" (Anonymous, 1991). At the time virtually all gene therapies were retroviral and were prepared as *ex vivo* somatic cell therapies. This was subsequently reviewed by Kessler et al. (1993). While the data for certain categories of information such as that regarding molecular biology were defined in previous guidance documents relating to rDNA products, the standards for preclinical and clinical development were less well defined. The field has advanced to include not only new vectors but also novel routs of administration. "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" was thus amended in 1996 (Leibert, 1996) to reflect both advancements in product development and more importantly the accumulation of safety information.

FDA regulations state that the sponsor must submit, in the IND, adequate information about pharmacological and toxicological studies of the drug including laboratory animals or *in vitro* studies on the basis of which the sponsor has considered that it is reasonably safe to conduct the proposed clinical investigation. For cellular and gene therapies, designing and conducting relevant preclinical safety testing has been a challenge to both the FDA and to the sponsors. For genes delivered using viral vectors, the safety of the vector system *per se* must be considered and evaluated.

The preclinical knowledge base is initially developed by designing studies to answer fundamental questions. The development of this knowledge base is generally applicable to most pharmaceuticals as well as biopharmaceuticals and includes data to support (i) the relationship of the dose to biological activity, (ii) the relationship of the dose to toxicity, (iii) the effect of route and/or schedule on activity or toxicity, and (iv) identification of the potential risks for subsequent clinical studies. These questions are considered in the context of indication and/or disease state. In addition there are often unique concerns in relation to the specific category or product class.

For cellular therapies safety concerns may include development of a database from studies specifically designed to answer questions relating to growth factor dependence, tumorigenicity, local and systemic toxicity, and effects on

host immune responses including immune activation and altered susceptibility to disease. For viral-mediated gene therapies, specific questions may relate to the potential for overexpression of the transduced gene, transduction of normal cells/tissues, genetic transfer to germ cells and subsequent alterations to the genome, recombination/rescue with endogenous virus, reconstitutions of replication competence, potential for insertional mutagenesis/malignant transformation, altered susceptibility to disease, and/or potential risk(s) to the environment.

To date cellular and gene therapy products submitted to FDA have included clinical studies indicated for bone marrow marking, cancer, cystic fibrosis, AIDS, and inborn errors of metabolism and infectious diseases. Of the current active INDs approximately 78% have been sponsored by individual investigators or academic institutions, and 22% have also been industry sponsored. In addition to the variety of clinical indications, the cell types have also been varied. Examples include tumor-infiltrating lymphocytes (TIL) and lymphocyte-activated killer (LAK) cells, selected cells from bone marrow and peripheral blood lymphocytes (e.g., stem cells), myoblasts, tumor cells, and encapsulated cells (e.g., islet cells and adrenal chromaffin cells).

### 2.8.1 Cellular Therapies

Since 1984 CBER has reviewed close to 300 somatic cell therapy protocols. Examples of the specific categories include manipulation, selection, mobilization, tumor vaccines, and other.

*Manipulation* Autologous, allogenic, or xenogenic cells which have been expanded, propagated, or manipulated or had their biological characteristics altered *ex vivo* (e.g., TIL or LAK cells; islet cells housed in a membrane).

*Selection* Products designed for positive or negative selection if autologous or allogenic cells intended for therapy (e.g., purging of tumor from bone marrow, selection of CD34+ cells).

*Mobilization* *In vivo* mobilization of autologous stem cells intended for transplantation.

*Tumor vaccines* Autologous or allogenic tumor cells which are administered as vaccines (e.g., tumor cell lines, tumor cell lysates, primary explant. See FDA (1993)). This group also includes autologous antigen-presenting cells pulsed with tumor-specific peptides or tumor cell lysates.

*Other* Autologous, allogenic, and xenogenic cells which do not specifically fit above. This group includes cellular therapies such as extracorporeal liver assist devices.

### 2.8.2 Gene Therapies

The types of vectors that have been used, or proposed, for gene transduction include retrovirus, adenovirus, adeno-associated viruses, other viruses (e.g., herpes, vaccinia, etc.), and plasmid DNA. Methods for gene introduction include *ex vivo* replacement, drug delivery, marker studies, and others and *in vivo* viral vectors, plasmid vectors, and vector producer cells.

### 2.8.3 *Ex Vivo*

*Replacement* Cells transduced with a vector expressing a normal gene in order to correct or replace the function of a defective gene

*Drug delivery* Cells transduced with a vector expressing a gene encoding a therapeutic molecule which can be novel or native to the host

*Marker studies* Cells (e.g., bone marrow, stem cells) transduced with a vector expressing a marker or reporter gene used to distinguish it from other similar host tissues

*Other* Products which do not specifically fit under above (e.g., tumor vaccines in which cells are cultured or transduced *ex vivo* with a vector)

### 2.8.4 *In Vivo*

*Viral vectors* The direct administration of a viral vector (e.g., retrovirus, adenovirus, adeno-associated virus, herpes, vaccinia) to patients

*Plasmid vectors* The direct administration of plasmid vectors with or without other vehicles (e.g., lipids) to patients

*Vector producer cells* The direct administration of retroviral vector producer cells (e.g., murine cells producing HTK vector) to patients

### 2.8.5 Preclinical Safety Evaluation

The goal of preclinical safety evaluation includes recommendation of an initial safe starting dose and safe dose-escalation scheme in humans, identification of potential target organ(s) of toxicity, identification of appropriate parameters for clinical monitoring, and identification of "at-risk" patient population(s). Therefore, when feasible, toxicity studies should be performed in relevant species to assess a dose-limiting toxicity. General considerations in study design include selection of the model (e.g., species, alternative model, animal model of disease), dose (e.g., route, frequency, and duration) and study end point (e.g., activity and/or toxicity).

The approach to preclinical safety evaluation of biotechnology-derived products, including novel cellular and gene therapies, has been referred to as the "case-by-case" approach. This approach is science based, data driven, and

flexible. The major distinction from past practices from traditional pharmaceuticals is that the focus is directed at asking specific questions across various product categories. Additionally, there is a consistent reevaluation of the knowledge base to reassess real or theoretical safety concerns and hence reevaluation of the need to answer the same questions across all product categories. In some cases there may even be conditions which may not need specific toxicity studies, for example, when there is a strong efficacy model which is rationally designed to answer specific questions and/or there is previous human experience with a similar product with respect to dose and regimen.

### 2.8.6 Basic Principles for Preclinical Safety Evaluation of Cellular and Gene Therapies

Biotechnology-derived products in general

- Use of product in animal studies that is comparable or the same as the product proposed for clinical trial(s)
- Adherence to basic principles of GLP to ensure quality of the study including a detailed protocol prepared prospectively
- Use of the same or similar route and method of administration as proposed for clinical trials (whenever possible)
- Determination of appropriate doses delivered based upon preliminary activity obtained from both *in vitro* and *in vivo* studies (i.e., finding a dose likely to be effective and not dangerous, a no-observed-adverse-effect level, and a dose causing dose-limiting toxicity)
- Selection of one or more species sensitive to the end point being measured, for example, infections or pathologic sequelae and/or biological activity or receptor binding
- Consideration of animal model(s) of disease that may be better to assess the contribution of changes in physiologic or underlying physiology to safety and efficacy
- Determination of affect on host immune response
- Localization/distribution studies—evaluation of target tissue, normal surrounding tissue, and distal tissue sites and any alteration in normal or expected distribution
- Local reactogenicity

### 2.8.7 Additional Considerations for Cellular Therapies

- Evaluation of cytopathogenicity
- Evaluation of signs of cell transformation/growth factor dependence effect on animal cells, normal human cells, and cells prone to transform easily
- Determination of alteration in cell phenotype, altered cell products, and/or function
- Tumorigenicity

### 2.8.8 Additional Considerations for Gene Therapies

- Determination of phenotype/activation state of effector cells
- Determination of vector/transgene toxicity
- Determination of potential transfer to germline
- *In vitro* challenge studies—evaluation of recombination or complementation, potential for "rescue" for subsequent infection with wild-type virus
- Determination of persistence of cells/vector
- Determination of potential for insertional mutagenesis (malignant transformation)
- Determination of environmental spread (e.g., viral shedding)

## 2.9 TOXICITY TESTING: SPECIAL CASES

On paper, the general case guidelines for the evaluation of the safety of drugs are relatively straightforward and well understood. However, there are also a number of special case situations under which either special rules apply or some additional requirements are relevant. The more common of these are summarized as follows.

### 2.9.1 Oral Contraceptives

Oral contraceptives are subject to special testing requirements. These have recently been modified so that in addition to those preclinical safety tests generally required, the following are also required (Berliner, 1974):

- A 3-year carcinogenicity study in beagles (this is a 1987 modification in practice from earlier FDA requirements and the 1974 publication)
- A rat reproductive (segment I) study including a demonstration of return to fertility

### 2.9.2 Life-Threatening Diseases (Compassionate Use)

Drugs to treat life-threatening diseases are not strictly held to the sequence of testing requirements as put forth in Table 2.3 because the potential benefit on any effective therapy in these situations is so high. In the early 1990s, this situation applied to AIDS-associated diseases and cancer. The development of more effective HIV therapies (protease inhibitors) has now made cancer therapy more the focus of these considerations. Though the requirements for safety testing prior to initial human trials are unchanged, subsequent requirements are flexible and subject to negotiation and close consultation with FDA's Division of Oncology (within CDER) (FDA, 1988). The more recent thinking on anticancer agents has been reviewed by DeGeorge et al. (1998). The preclinical studies that will be required to support clinical trials and

marketing of new anticancer agents will depend on the mechanism of action and the target clinical population. Toxicity studies in animals will be required to support initial clinical trials. These studies have multiple goals:

- Determine a starting dose for clinical trials
- Identify target organ toxicity and assess recovery
- Assist in the design of clinical dosing regimens

The studies should generally conform to the protocols recommended by the National Cancer Institute, as discussed by Greishaber (1991). In general, it can be assumed that most antineoplastic cytotoxic agents will be highly toxic. Two studies are essential to support initial clinical trials (IND phase) in patients with advanced disease. These are studies of 5–14 days in length, but with longer recovery periods. A study in rodents is required that identifies those doses that produce either life-threatening or nonlife-threatening toxicity. Using the information from this first study, a second study in nonrodents (generally the dog) is conducted to determine if the tolerable dose in rodents produces life-threatening toxicity. Doses are compared on a milligram-per-square-meter basis. The starting dose in initial clinical trials is generally one-tenth of that required to produce severe toxicity in rodents (STD10) or one-tenth the highest dose in nonrodents that does not cause severe irreversible toxicity. While not required, information on PK parameters, especially data comparing the plasma concentration associated with toxicity in both species, is very highly regarded. Special attention is paid to organs with high cell division rates, bone marrow, testes, lymphoid tissue testing, and gastrointestinal (GI) tract. As these agents are almost always given intravenously, special attention needs to be given relatively early in development to intravenous irritation and blood compatibility study. Subsequent studies to support the NDA will be highly tailored, depending on the following:

- Therapeutic indication and mechanism of action
- The results of the initial clinical trials
- The nature of the toxicity
- Proposed clinical regimen

Even at the NDA stage, toxicity studies with more than 28 days of dosing are rarely required. While not required for the IND, assessment of genotoxicity and developmental toxicity will need to be addressed. For genotoxicity, it will be important to establish the ratio between cytotoxicity and mutagenicity. *In vivo* models, for example, the mouse micronucleus test, can be particularly important in demonstrating the lack of genotoxicity at otherwise subtoxic doses. For developmental toxicity, ICH stage C–D studies (traditionally known as segment II studies for teratogenicity in rat and rabbits) will also be necessary.

The emphasis of this discussion has been on purely cytotoxic neoplastic agents. Additional considerations must be given to cytotoxic agents that are administered under special circumstances: those that are photoactivated, delivered as liposomal emulsions, or delivered as antibody conjugates. These types of agents will require additional studies. For example, a liposomal agent will need to be compared to the free agent and a blank liposomal preparation. There are also studies that may be required for a particular class of agents. For example, anthracyclines are known to be cardiotoxic, so comparison of a new anthracycline agent to previously marketed anthracyclines will be expected.

In addition to antineoplastic, cytotoxic agents, there are cancer therapeutic or preventative drugs that are intended to be given on a chronic basis. This includes chemopreventatives, hormonal agents, immunomodulators, etc. The toxicity assessment studies on these will more closely resemble those of more traditional pharmaceutical agents. Chronic toxicity, carcinogenicity, and full developmental toxicity (ICH A–B, C–D, E–F) assessments will be required. For a more complete review, the reader is referred to DeGeorge et al. (1998).

### 2.9.3 Optical Isomers

The FDA (and like regulatory agencies, as reviewed by Daniels et al. (1997)) has become increasingly concerned with the safety of stereoisomeric or chiral drugs. Stereoisomers are molecules that are identical to one another in terms of atomic formula and covalent bonding but differ in the three-dimensional projections of the atoms. Within this class are those molecules that are nonsuperimposable mirror images of one another. These are called enantiomers (normally designated as R- or S-). Enantiomeric pairs of a molecule have identical physical and chemical characteristics except for the rotation of polarized light. Drugs have generally been mixtures of optical isomers (enantiomers), because of the difficulties in separating the isomers. It has become apparent in recent years, however, that these different isomers may have different degrees of both desirable therapeutic and undesirable toxicologic effects. Technology has also improved to the extent that it is now possible to perform chiral specific syntheses, separations, and/or analyses. It is now highly desirable from a regulatory (FDA, 1988; De Camp, 1989; Anonymous, 1992/2015; FDA, 2015) basis to develop a single isomer unless all isomers have equivalent pharmacological and toxicologic activity. The FDA has divided enantiomeric mixtures in the following categories:

- Both isomers have similar pharmacologic activity, which could be identical, or they could differ in the degrees of efficacy.

- One isomer is pharmacologically active, while the other is inactive.
- Each isomer has completely different activity.

During preclinical assessment of an enantiomeric mixture, it may be important to determine to which of these three classes it belongs. The pharmacological and toxicological a properties of the individual isomers should be characterized. The PK profile of each isomer should be characterized in animal models with regard to disposition and interconversion. It is not at all unusual for each enantiomer to have a completely different PK behavior.

If the test article is an enantiomer isolated from a mixture that is already well characterized (e.g., already on the market), then appropriate bridging guides need to be performed which compare the toxicity of the isomer to that of the racemic mixture. The most common approach would be to conduct a subchronic (3 months) and a segment II type teratology study with an appropriate "positive" control group which received the racemate. In most instances no additional studies would be required if the enantiomer and the racemate did not differ in toxicity profile. If, on the other hand, differences are identified, the reasons for this difference need to be investigated and the potential implications for human subjects need to be considered.

### 2.9.4 Special Populations: Pediatric and Geriatric Claims

Relatively few drugs marketed in the United States (~20%) have pediatric dosing information available. Clinical trials had rarely been done specifically on pediatric patients. Traditionally, dosing regimens for children have been derived empirically by extrapolating on the basis of body weight or surface area. This approach assumes that the pediatric patient is a young adult, which simply may not be the case. There are many examples of how adults and children differ qualitatively in metabolic and/or pharmacodynamic responses to pharmaceutical agents. In their review, Shacter and DeSantis (1998) state, "The benefit of having appropriate usage information in the product label is that health care practitioners are given the information necessary to administer drugs and biologics in a manner that maximizes safety, minimizes unexpected adverse events, and optimizes treatment efficacy. Without specific knowledge of potential drug effects, children may be placed at risk. In addition, the absence of appropriate proscribing information, drugs and biologics that represent new therapeutic advances may not be administered to the pediatric population in a timely manner." In response to the need for pediatric information, the FDA had developed a pediatric plan. This two-phase plan called first for the development of pediatric information on marketed drugs. The second phase focused on new drugs. The implementation of the plan was to be coordinated by the Pediatric Subcommittee of the Medical Policy Coordinating Committee of CDER. The Pediatric Use Labeling Rule was a direct result of phase I in 1994 (PhRMA, 1998). Phase II resulted in 1997 from a proposed rule entitled "Pediatric Patients: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologics." Soon after this rule was proposed, the FDAMA of 1997 was passed. FDAMA contained provisions that specifically addressed the needs and requirements for the development of drugs for the pediatric population.

The FDAMA bill essentially codified and expanded several regulatory actions initiated by the FDA during the 1990s. Among the incentives offered by the bill, companies will be offered an additional 6 months of patent protection for performing pediatric studies (clinical trials) on already approved products. In fact, the FDA was mandated by the FDAMA to develop a list of over 500 drugs for which additional information would produce benefits for pediatric patients. The FDA is supposed to provide a written request for pediatric studies to the manufacturers (Hart, 1999).

In response to the pediatric initiatives, the FDA has published policies and guidelines and conducted a variety of meetings. CDER has established a website (http://www.fda.gov/cder/pediatric) which lists three pages of such information. Interestingly, the focus has been on clinical trials, and almost no attention has been given to the preclinical toxicology studies that may be necessary to support such trials. There are three pages of documents on the pediatric website. None appear to address the issue of appropriate testing. This is a situation that is just now being addressed and is in a great deal of flux.

In the absence of any guidelines from the agency for testing drugs in young or "pediatric" animals, one must fall back on the maxim of designing a program that makes the most scientific sense. As a guide, the FDA designated levels of postnatal human development and the approximate equivalent ages (in the author's considered opinion) in various animal models are given in Table 2.9. The table is somewhat inaccurate, however, because of difference in the stages of development at birth. A rat is born quite underdeveloped when compared to a human being. A 1-day-old rat is not equivalent to a 1-day-old full-term human infant. A 4-day-old rat would be more appropriate. In terms of development, the pig may be the best model of those listed; however, one should bear in mind that different organs have different developmental schedules in different species.

Table 2.9 can be used as a rough guide in designing toxicity assessment experiments in developing animals. In designing of the treatment period, one needs to consider not only the dose and the proposed course of clinical treatment but also the proposed age of the patient and whether or not an equivalent dosing period in the selected animal model covers more than one developmental stage. For example, if the proposed patient population is human infants, initiating a

**TABLE 2.9 Comparison of Postnatal Development Stages**

| Stage | Human | Rat | Dog | Pig |
|---|---|---|---|---|
| Neonate | Birth to 1 month | Birth to 1 week | Birth to 3 weeks | Birth to 2 weeks |
| Infant | 1 month–2 years | 1–3 weeks | 3–6 weeks | 2–4 weeks |
| Child | 2–12 years | 3–9 weeks | 6 weeks–5 months | 4 weeks–4 months |
| Adolescent | 12–16 years | 9–13 weeks | 5–9 months | 4–7 months |
| Adult | Over 16 years | Over 13 weeks | Over 9 months | Over 7 months |

toxicity study of the new pharmaceutical agent in 3-day-old rats is not appropriate. Furthermore, if the proposed course of treatment in adult children is 2 weeks, it is unlikely that this would cross over into a different developmental stage. A 2-week treatment initiated in puppies, however, might easily span two developmental stages. Thus, in designing an experiment in young animals, one must carefully consider the length of the treatment period balancing the developmental age of the animal model and the proposed length of clinical treatment. Where appropriate (infant animals), one needs to also assess changes in standard developmental landmarks (e.g., eye opening, pinnae eruption, external genitalia development, etc.) as well as the more standard indicators of target organ toxicity. The need for maintaining the experimental animals past the dosing period, perhaps into sexual maturity, to assess recovery or delayed effects needs also to be carefully considered.

To summarize, the current status of assessment of toxicity in postnatal mammals, in response to the pediatric initiatives covered in FDAMA, is an extremely fluid situation. One needs to carefully consider a variety of factors in designing the study and should discuss proposed testing programs with the appropriate office at CDER.

Drugs intended for use in the elderly, like those intended for the very young, may also have special requirements for safety evaluation, but geriatric issues were not addressed in the FDAMA of 1997. The FDA has published a separate guidance document for geriatric labeling (CDER and CBER, 2001). As was the case with pediatric guidance, this document does not address preclinical testing. With the elderly, the toxicological concerns are quite different than the developmental concerns associated with pediatric patients. With the elderly, one must be concerned with the possible interactions between the test article and compromised organ function. The FDA had previously issued a guidance for clinically examining clinical safety of new pharmaceutical agents in patients with compromised renal and/or hepatic function (CDER, 1989). The equivalent ICH guideline (S5A) was issued in 1994. Whether this type of emphasis will require toxicity testing in animal models with specifically induced organ insufficiency remains to be seen. In the interim, we must realize that there is tacit evaluation of test-article-related toxicity in geriatric rodents for those agents that undergo 2-year carcinogenicity testing. As the graying of America continues, labeling for geriatric use may become more of an issue in the future.

As presented in Table 2.10 there are four special case INDs that lead to earlier approval of drugs for special cases. The prototype for these would be the orphan drug route.

### 2.9.5 Orphan Drugs

The development of sophisticated technologies, coupled with the rigors and time required for clinical and preclinical testing, has made pharmaceutical development very expensive. In order to recoup such expenses, pharmaceutical companies have tended to focus on therapeutic agents with large potential markets. Treatments for rare but life-threatening diseases have been "orphaned" as a result. An orphan product is defined as one targeted at a disease which affects 200,000 or fewer individuals in the United States. Alternatively, the therapy may be targeted for more than 200,000, but the developer would have no hope of recovering the initial investment without exclusivity. The Orphan Drug Act (ODA) of 1983 was passed in an attempt to address this state of affairs. Currently applicable regulations were put in place in 1992 and amended in 2013 (Anonymous, 2013). In 1994, there was an attempt in Congress to amend the Act, but it failed to be passed into law. The current regulations are administered by the Office of Orphan Products Development (OOPD). The Act offers the following incentives to encourage the development of products to treat rare diseases:

- Seven-year exclusive market following the approval of a product for an orphan disease
- Written protocol assistance from the FDA
- Tax credits for up to 50% of qualified clinical research expenses
- Available grant to support pivotal clinical trials

As reviewed by Haffner (1998), other developed countries have similar regulations.

There are significant misconceptions about the orphan drug process (Tambuyzer, 2010). The ODA did not change the requirements of testing drug products. The nonclinical testing programs are similar to those used for more conventional products. They will undergo the same FDA review process. A major difference, however, is the involvement of the OPD. A sponsor must request OPD review. Once OPD determines that a drug meets the criteria for orphan drug

**TABLE 2.10 Comparison of FDA's Expedited Programs for Serious Conditions (CDER and CBER, 2014)**

| Nature of program | Fast-Track | Breakthrough Therapy | Accelerated Approval | Priority Review |
|---|---|---|---|---|
| | Designation | Designation | Approval Pathway | Designation |
| Reference | • Section 506(b) of the FD&C Act, as added by Section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by Section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) | • Section 506(a) of the FD&C Act, as added by Section 902 of FDASIA | • 21 CFR Part 314, Subpart H<br>• 21 CFR Part 601, Subpart E<br>• Section 506(c) of the FD&C Act, as amended by Section 901 of FDASIA | • Prescription Drug User Fee Act of 1992 |
| Qualifying criteria | • A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR<br>• A drug that has been designated as a qualified infectious disease product[a] | • A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant end point(s) over available therapies | • A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate end point that is reasonably likely to predict clinical benefit or on a clinical end point that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical end point) | • An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR<br>• Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A[b] OR<br>• An application for a drug that has been designated as a qualified infectious disease product[c] OR<br>• Any application or supplement for a drug submitted with a priority review voucher[d] |
| When to submit request | • With IND or after<br>• Ideally, no later than the pre-BLA or pre-NDA meeting | • With IND or after<br>• Ideally, no later than the end-of-phase II meeting | • The sponsor should ordinarily discuss the possibility of accelerated approval with the review division during development, supporting, for example, the use of the planned end point as a basis for approval and discussing the confirmatory trials, which should usually be already under way at the time of approval | • With original BLA, NDA, or efficacy supplement |
| Timelines for FDA response | • Within 60 calendar days of receipt of the request | • Within 60 calendar days of receipt of the request | • Not specified | • Within 60 calendar days of receipt of original BLA, NDA, or efficacy supplement |

(*Continued*)

**TABLE 2.10 (Continued)**

| Nature of program | Fast-Track | Breakthrough Therapy | Accelerated Approval | Priority Review |
|---|---|---|---|---|
| | Designation | Designation | Approval Pathway | Designation |
| Features | • Actions to expedite development and review<br>• Rolling review | • Intensive guidance on efficient drug development<br>• Organizational commitment<br>• Rolling review<br>• Other actions to expedite review | • Approval based on an effect on a surrogate end point or an intermediate clinical end point that is reasonably likely to predict a drug's clinical benefit | • Shorter clock for review of marketing application (6 months compared with the 10-month standard review)[e] |
| Additional considerations | • Designation may be rescinded if it no longer meets the qualifying criteria for fast track[f] | • Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy[g] | • Promotional materials<br>• Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit<br>• Subject to expedited withdrawal | • Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing |

*Source*: Extracted from CDER and CBER (2014).

[a] Title VIII of FDASIA, "Generating Antibiotic Incentives Now (GAIN)," provides incentives for the development of antibacterial and antifungal drugs for human use intended to treat serious and life-threatening infections. Under GAIN, a drug may be designated as a qualified infectious disease product (QIDP) if it meets the criteria outlined in the statute. A drug that receives QIDP designation is eligible under the statute for fast-track designation and priority review. However, QIDP designation is beyond the scope of this guidance.

[b] Any supplement to an application under Section 505 of the FD&C Act that proposes a labeling change pursuant to a report on a pediatric study under this section shall be considered a priority review supplement per Section 505A of the FD&C Act as amended by Section 5(b) of the Best Pharmaceuticals for Children Act.

[c] See footnote a above.

[d] Any application or supplement that is submitted with a priority review voucher will be assigned a priority review. Priority review vouchers will be granted to applicants of applications for drugs for the treatment or prevention of certain tropical diseases, as defined in Section 524(a)(3) and (a)(4) of the FD&C Act and for treatment of rare pediatric diseases as defined in Section 529(a)(3) of the FD&C Act.

[e] As part of its commitments in PDUFA V, the FDA has established a review model, the Program. The Program applies to all new molecular entity NDAs and original BLAs, including applications that are resubmitted following a refuse-to-file action, received from October 1, 2012, through September 30, 2017. For applications filed by FDA under the Program, the PDUFA review clock will begin at the conclusion of the 60 calendar day filing review period that begins on the date of FDA receipt of the original submission.

[f] A sponsor may also withdraw fast-track designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see Section A.5).

[g] A sponsor may also withdraw breakthrough therapy designation if the designation is no longer supported by emerging data or the drug development program is no longer being pursued (see Section B.5).

status, it will work with the sponsor to provide the assistance required under the Act. The ODA does not review a product for approval. The IND/NDA process is still handled by the appropriate reviewing division (e.g., Cardiovascular) for formal review. The Act does not waive the necessity for submission of an IND, not for the responsibility of toxicological assessment. As always, in cases where there is ambiguity, a sponsor may be well served to request a pre-IND meeting at the appropriate division to discuss the acceptability of a toxicology assessment plan.

### 2.9.6 Botanical Drug Products

There is an old saying, "What goes around comes around," and so it is with botanicals. At the beginning of the twentieth century, most marketed pharmaceutical agents were botanical in origin. For example, aspirin was first isolated from willow bark. These led the way in the middle part of the century, for reasons having to do with patentability, manufacturing costs, standardization, selectivity, and potency. The dawning of the twenty-first century has seen a grassroots return to botanical preparations (also sold as herbals or dietary supplements). These preparations are being marketed to the lay public as "natural" supplements to the nasty synthetic chemicals now proscribed as pharmaceutical products. In 1994, the Dietary Supplement Health and Education Act was passed which permitted the marketing of dietary supplements (including botanicals) with limited submissions to the FDA (Wu et al., 2000). If a producer makes a claim that an herbal preparation is beneficial to a specific part of the body (e.g., enhanced memory), then it may be marketed after a 75-day period of FDA review but without formal approval. On the other hand, if any curative properties are claimed, then the botanical will be regulated as a drug and producers will be required to follow the IND/NDA process. In 1997 and 1998 combined, some 26 INDs were filed for botanical products (Wu et al., 2000).

The weakness in the current regulation has to do with its ambiguity. The line between a beneficial claim and a curative claim is sometimes difficult to draw. What is the difference, for example, between an agent that enhances memory and one that prevents memory loss? Given the number of products and claims hitting the shelves every day, this situation will probably demand increased regulatory scrutiny in the future.

### 2.9.7 Types of New Drug Applications (NDAs)

Actual product approvals for drugs are one form or another of NDA. While in this volume we focus on the traditional (505(b)(1)), there are two others for small molecules—505(b)(2) Applications and Abbreviated New Drug Application (ANDA) (for generic drug applications). These have minimal if any nonclinical safety requirements. While these are US FDA terms for the non-NME drug approvals, equivalents exist in other major regulatory paradigms (see, e.g., EOC Directive 2001/83/EC, amended in July of 2008).

## 2.10 INTERNATIONAL PHARMACEUTICAL REGULATION AND REGISTRATION

### 2.10.1 International Conference on Harmonization

The ICH was established to make the drug regulatory process more efficient in the United States, Europe, and Japan. The US involvement grew out of the fact that the United States is party to the General Agreement on Tariffs and Trade, which included the Agreement on Technical Barriers to Trade, negotiated in the 1970s, to encourage reduction of nontariff barriers to trade (Barton, 1998). The main purpose of ICH is, through harmonization, to make new medicines available to patients with a minimum of delay. More recently, the need to harmonize regulation has been driven, according to ICH, by the escalation of the cost of R&D. The regulatory systems in all countries have the same fundamental concerns about safety, efficacy, and quality, yet sponsors had to repeat many time-consuming and expensive technical tests to meet country-specific requirements. Secondarily, there was a legitimate concern over the unnecessary use of animals. Conference participants include representatives from the drug regulatory bodies and research-based pharmaceutical industrial organizations of three regions; the European Union (EU), the United States, and Japan were over 90% of world's pharmaceutical industry. Representation is summarized in Table 2.11. The biennial conference met regularly

**TABLE 2.11 ICH Representation**

| Country/Region | Regulatory | Industry |
|---|---|---|
| European Union | European Commission (2) | European Federation of Pharmaceutical Industries and Associations (2) |
| Japan | Ministry of Health and Welfare (2) | Japan Pharmaceutical Manufacturers Association (2) |
| United States | Food and Drug Administration (2) | Pharmaceutical Research and Manufacturers of America (2) |
| Observing organizations | World Health Organization, European Free Trade Association, Canadian Health Protection Branch | International Federation of Pharmaceutical Manufactures & Associations (2): also provides the secretariat |

Numbers in parentheses are number of representatives on the ICH Steering Committee.

**TABLE 2.12 Steps in ICH Guideline Development and Implementation**

| | |
|---|---|
| 1 | Building scientific consensus in joint regulatory/industry expert working groups |
| 2 | Agreement by the steering committee to release the draft consensus text for wider consultation |
| 3 | Regulatory consultation in the three regions. Consolidation of the comments |
| 4 | Agreement on a harmonized ICH guideline; adopted by the regulators[a] |
| 5 | Implementation in the three ICH regions[a] |

[a] ICH (1997).

beginning in 1991, rotating between sites in the United States, Europe, and Japan.

The ICH meets its objectives by issuing guidelines for the manufacturing, development, and testing of new pharmaceutical agents that are acceptable to all three major parties. For each new guideline, the ICH Steering Committee establishes an expert working group with representation from each of the six major participatory ICH bodies. Each new draft guideline goes through the five various steps of review and revision summarized in Table 2.12. So far, ICH has proposed or adopted over 40 safety, efficacy, and quality guidelines (listed in Table 2.13) for use by the drug regulatory agencies in the United States, Europe, and Japan. Those guidelines specifically applying to nonclinical drug safety evaluation, in their most current state, are listed in Table 2.14.

The guidelines are organized under broad categories: the "E" series having to do with clinical trials, the "Q" series having to do with quality (including chemical manufacturing and control as wells as traditional GLP issues), and the "S" series having to do with safety. Guidelines may be obtained from the ICH secretariat, c/o of IFPMA, 30 rue de St.-Jean, PO Box 9, 1211 Geneva 18, Switzerland, or may be downloaded directly from the ICH website (http://www.ich.org/products/guidelines.html). They are also published in the Federal Register. It is the guidelines of the "S" series that will have the most impact on toxicologists. The biggest changes having to do with toxicological assessment are summarized as follows.

***2.10.1.1 Carcinogenicity Studies*** Carcinogenicity studies are covered in Guidelines S1A, S1B, and S1C. The guidelines are almost more philosophical than they are technical. In comparison to the EPA guidelines, for example, the ICH guidelines contain little in the way on concrete study criteria (e.g., the number of animals, the necessity for clinical chemistry, etc.). There is discussion on when carcinogenicity studies should be done, whether two species are more appropriate than one, and how to set dosages on the basis of human clinical PK data. The major changes being wrought by these guidelines are the following:

- Only one 2-year carcinogenicity study should be generally required. Ideally, the species chosen should be the one most like man in terms of metabolic transformations of the test article.
- The traditional second long-term carcinogenicity study can be replaced by a shorter-term alternative model. In practical terms, this guideline is beginning to result in sponsors conducting a 2-year study in the rat and a 6-month study in an alternative mouse model, such as the P53 or the TG.AC genetically manipulated mouse strains.
- In the absence of target organ toxicity with which to set the high dose at the maximally tolerated dose, the high dose can be set at the dose that produces an area under the curve (AUC). This is 25-fold higher than that obtained in human subjects.

***2.10.1.2 Chronic Toxicity*** Traditionally, chronic toxicity of new pharmaceuticals in the United States was assessed in studies of 1-year duration in both the rodent and the nonrodent species of choice. The European view was that studies of 6 months are generally sufficient. The resulting guideline (S4A) was a compromise. Studies of 6-month duration were recommended for the rodent, as rodents would also be examined in 2-year studies. For the nonrodent (dog, nonhuman primate, and pig), studies of 9-month duration were recommended.

***2.10.1.3 Developmental and Reproductive Toxicity*** This was an area in which there was considerable international disagreement and the area in which ICH has promulgated the most technically detailed guidelines (S5A and S5B). Some of the major changes include the following:

- The traditional segment I, II, and III nomenclature has been replaced with different nomenclature, as summarized in Table 2.15.
- The dosing period of the pregnant animals during studies on embryonic development (traditional segment II) studies has been standardized.
- New guidelines for fertility assessment (traditional segment I) studies that have shortened the premating dosing schedule (e.g., in male rats from 10 to 4 weeks). There has been an increased interest in assessment of spermatogenesis and sperm function.
- The new guidelines allow for a combination of studies in which the end point typically assessed in the traditional segment II and segment III studies is now examined under a single protocol.

For a more complete review of the various study designs, the reader is referred to the review by Manson (1994).

**TABLE 2.13 International Conference on Harmonization Guidelines**

| References | Guideline | Date |
|---|---|---|
| E1 | The Extent of Population Exposure to Assess Clinical Safety | October 1994 |
| E2A | Clinical Safety Data Management: Definitions and Standards for Expedited Reporting | October 1994 |
| E2B(R3) | Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports | November 2014 |
| E2C(R2) | Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs | November 2012 |
| E2D | Definitions and Standards for Expedited Reporting | November 2003 |
| E2E | Pharmacovigilance Planning | November 2004 |
| E2F | Development Safety Update Report | August 2010 |
| E3 | Structure and Content of Clinical Study Reports | November 1995 |
| E4 | Dose-Response Information to Support Drug Registration | March 1994 |
| E5(R1) | Ethnic Factors in the Acceptability of Foreign Clinical Data | February 1998 |
| E6(R1) | Good Clinical Practice | May 1996 (R2 draft integrated addendum: June 2015) |
| E7 | Studies in Support of Special Populations: Geriatrics | June 1993 |
| E8 | Guidance on General Considerations for Clinical Trials; Notice | July 1997 |
| E9 | Guideline on Statistical Principles for Clinical Trials; Notice of Availability | February 1998 |
| E10 | Choice of Control Group and Related Issues in Clinical Trials | July 2000 |
| E11 | Clinical Investigation of Medicinal Products in the Pediatric Population | July 2000 (R1 concept paper: August 2014) |
| E12 | Principles for Clinical Evaluation of New Antihypertensive Drugs | March 2000 |
| E14 | The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs | May 2005 |
| E15 | Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories | November 2007 |
| E16 | Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions | August 2010 |
| E17 | General Principle on Planning/Designing Multi-Regional Clinical Trials | May 2016 (Current Step 2 Version) |
| E18 | Draft Guideline: Genomic Sampling and Management of Genomic Data | December 2015 |
| M3(R2) | Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals | June 2009 |
| Q1A(R2) | Stability Testing of New Drug Substances and Products | February 2003 |
| Q1B | Stability Testing of New Drug Substances and Products | November 1996 |
| Q1C | Stability Testing for New Dosage Forms | November 1996 |
| Q1D | Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products | February 2002 |
| Q1E | Evaluation of Stability Data | February 2003 |
| Q2(R1) | Validation of Analytical Procedures: Text and Methodology | October 1994 |
| Q3A(R2) | Impurities in New Drug Substances | October 2006 |
| Q3B(R2) | Impurities in New Drug Products | June 2006 |

(*Continued*)

**TABLE 2.13 (Continued)**

| References | Guideline | Date |
|---|---|---|
| Q3C(R5) | Impurities: Guideline for Residual Solvents | February 2011 (R6 draft revision: June 2015) |
| Q3D | Guidelines for Elemental Impurities | December 2014 |
| Q4 | Pharmacopoeias | November 2007 |
| Q4A | Pharmacopoeial Harmonisation | November 2007 |
| Q4B | Evaluation and Recommendation of Pharmacopeial Texts | November 2007 |
| Q4B Annex 1(R1) | Evaluation and Recommendation of Pharmacopoeial Texts: Residue on Ignition/Sulphated Ash General Chapter | September 2010 |
| Q4B Annex 2(R1) | Evaluation and Recommendation of Pharmacopoeial Texts: Test for Extractable Volume of Parenteral Preparations General Chapter | September 2010 |
| Q4B Annex 3(R1) | Evaluation and Recommendation of Pharmacopoeial Texts: Test for Particulate Contamination: Sub-Visible Particles General Chapter | September 2010 |
| Q4B Annex 4A(R1) | Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter | September 2010 |
| Q4B Annex 4B(R1) | Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter | September 2010 |
| Q4B Annex 4C(R1) | Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparation Substances for Pharmaceutical Use General Chapter | September 2010 |
| Q4B Annex 5(R1) | Disintegration Test General Chapter | September 2010 |
| Q4B Annex 6 | Uniformity of Dosage Units General Chapter | November 2013 |
| Q4B Annex 7(R2) | Dissolution Test General Chapter | November 2010 |
| Q4B Annex 8(R1) | Sterility Test General Chapter | September 2010 |
| Q4B Annex 9(R1) | Tablet Friability General Chapter | September 2010 |
| Q4B Annex 10(R1) | Polyacrylamide Gel Electrophoresis General Chapter | September 2010 |
| Q4B Annex 11 | Capillary Electrophoresis General Chapter | June 2010 |
| Q4B Annex 12 | Analytical Sieving General Chapter | June 2010 |
| Q4B Annex 13 | Bulk Density and Tapped Density of Powders General Chapter | June 2012 |
| Q4B Annex 14 | Bacterial Endotoxins Test General Chapter | October 2012 |
| Q5A(R1) | Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin | September 1999 |

(*Continued*)

**TABLE 2.13 (Continued)**

| References | Guideline | Date |
|---|---|---|
| Q5B | Quality of Biotechnology Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Product | November 1995 |
| Q5C | Quality of Biotechnological Products: Stability Testing of Biotechnological/Biology Products | November 1995 |
| Q5D | Availability of Draft Guideline on Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products | July 1997 |
| Q5E | Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process | November 2004 |
| Q6A | Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (including Decision Trees) | October 1999 |
| Q6B | Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products | March 1999 |
| Q7 | Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients | November 2000 |
| Q8(R2) | Pharmaceutical Development | August 2009 |
| Q9 | *Quality Risk Management* | November 2005 |
| Q10 | *Pharmaceutical Quality System* | June 2008 |
| Q11 | Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) | May 2012 |
| Q12 | Final Concept Paper: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management | July 2014 |

*See Table* 2.14 *for current safety guidance list*

While they were not quite as sweeping in approach as the aforementioned guidelines, a toxicologist working in pharmaceutical safety assessment should become familiar with the all the other ICH guidelines in the S series.

In an interesting recent article, Ohno (1999) discussed not the harmonization of nonclinical guidelines but also the need to harmonize the timing of nonclinical tests in relation to the conduct of clinical trials. For example, there are regional differences in the inclusion of women of childbearing potential in clinical trials. In the United States, including woman in such trials is becoming more important, and therefore evaluation of embryo-fetal development will occur earlier in the drug development process than in Japan. Whether or not such timing or staging of nonclinical tests becomes part of an ICH guideline in the near future remains to be established.

### 2.10.2 Other International Considerations

The United States is the single largest pharmaceutical market in the world. But the rest of the world (particularly, but not limited to the second and third largest markets, Japan and the EU) represents in aggregate a much larger market, so no one develops a new pharmaceutical for marketing in just the United States. The effort at harmonization (exemplified by the ICH) has significantly reduced differences in requirements for these other countries, but certainly not obliterated them. Though a detailed understanding of their regulatory schemes is beyond this volume, the bare bones and differences in toxicology requirements are not.

***2.10.2.1 European Union*** The standard EU toxicology and pharmacologic data requirements for a pharmaceutical include:

- Single-dose toxicity
- Repeat-dose toxicity (subacute and chronic trials)
- Reproduction studies (fertility and general reproductive performance, embryotoxicity, and peri-/postnatal toxicity)
- Mutagenic potential (*in vitro* and *in vivo*)
- Carcinogenicity
- Pharmacodynamics
  - Effects related to proposed drug indication
  - General pharmacodynamics
  - Drug interactions
- Pharmacokinetics
  - Single dose
  - Repeat dose

**TABLE 2.14 ICH Current Guidelines Governing Nonclinical Safety Evaluation**

| Reference Number and Classification | Title | Adopted Originally | Revisions | Link to Document |
|---|---|---|---|---|
| S1 Carcinogenicity studies | Rodent Carcinogenicity Studies for Human Pharmaceuticals | November 14, 2012 Endorsed as Final Concept Paper | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1/S1_Concept_Paper_14_November_2012.pdf |
| S1A Carcinogenicity studies | Guideline on the Need for Carcinogenicity Study of Pharmaceuticals | November 29, 1995 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1A/Step4/S1A_Guideline.pdf |
| S1B Carcinogenicity studies | Testing for Carcinogenicity of Pharmaceuticals | July 16, 1997 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1B/Step4/S1B_Guideline.pdf |
| S1C(R2) Carcinogenicity studies | Dose Selection for Carcinogenicity Studies of Pharmaceuticals | October 27, 1994 | R1: November, 2005<br>R2: March 11, 2008 | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S1C_R2/Step4/S1C_R2__Guideline.pdf |
| S2(R1) Genotoxicity studies | Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use | November 9, 2011 | The tripartite harmonized ICH guideline was finalized under *Step 4* in November 2011. It replaces and combines the ICH S2A and S2B guidelines | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4.pdf |
| S3A Toxicokinetics and pharmacokinetics | Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies | October 27, 1994 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S3A/Step4/S3A_Guideline.pdf |
| S3B Toxicokinetics and pharmacokinetics | Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies | October 27, 1994 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S3B/Step4/S3B_Guideline.pdf |
| S4 Toxicity testing | Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing) | September 2, 1998 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S4/Step4/S4_Guideline.pdf |
| S5(R2) Reproductive toxicology | Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility | June 24, 1993 | Addendum dated November 9, 2000 incorporated in November 2005<br>R3: Concept paper endorsed by steering | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5/Step4/S5_R2__Guideline.pdf |
| S6(R1) Biotechnological products | Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals | July 16, 1997 | Addendum dated June 12, 2011 incorporated at the end of June 2011 | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S6_R1/Step4/S6_R1_Guideline.pdf |

| | | | | |
|---|---|---|---|---|
| S7A<br>Pharmacology studies | Safety Pharmacology Studies for Human Pharmaceuticals | November 8, 2000 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S7A/Step4/S7A_Guideline.pdf |
| S7B<br>Pharmacology studies | The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals | May 12, 2005 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S7B/Step4/S7B_Guideline.pdf |
| S8<br>Immunotoxicology studies | Immunotoxicity Studies for Human Pharmaceuticals | September 15, 2005 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S8/Step4/S8_Guideline.pdf |
| S9<br>Nonclinical evaluation for anticancer pharmaceuticals | Nonclinical Evaluation for Anticancer Pharmaceuticals | October 29, 2009 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S9/Step4/S9_Step4_Guideline.pdf |
| S10<br>Photosafety evaluation | Photosafety Evaluation of Pharmaceuticals | November 13, 2013 | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S10/S10_Step_4.pdf |
| S11<br>Juvenile toxicity | Nonclinical Safety Testing in Support of Development of Pediatric Medicines | November 10, 2014<br>Endorsed as final concept paper | N/A | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S11/S11_Final_Concept_Paper_10_November_2014.pdf |
| M3R2<br>Nonclinical safety studies | Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals | July 16, 1997 | R1: November 9, 2000<br>R2: June 11, 2009 | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf |
| M7R1<br>Genotoxic impurities | Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk *And* Addendum | June 23, 2014 | R1: June 9, 2015 | http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Step_4.pdf *and* http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_Addendum_Step_2.pdf |
| Updated April 26, 2016 | | | | |
| All guidelines may also be accessed through the ICH website at http://www.ich.org/products/guidelines.html | | | | |

**TABLE 2.15 Comparison of Traditional and ICH Guidelines for Reproductive and Developmental Toxicology**

| Traditional Protocol | Stages Covered | ICH Protocol | Dosing Regimen |
|---|---|---|---|
| Segment I (rats) | A. Premating to conception<br>B. Conception to implantation | Fertility and early embryonic development, including implantation | Males: 4 weeks premating, mating (1–3 weeks) plus 3 weeks postmating<br>Females: 2 weeks premating, mating through day 7 of gestation |
| Segment II (rabbits) | C. Implantation to closure of hard palate<br>D. Closure of hard palate to the end of pregnancy | Embryo-fetal development | Females: day 6–20 of pregnancy |

| Study Title | Termination | Endpoints: In-Life | Endpoints: Postmortem |
|---|---|---|---|
| Fertility and early embryonic development, including implantation | Females: Day 13–15 of pregnancy<br>Males: Day after completion of dosing | Clinical signs and mortality<br>Body weights and feed intake<br>Vaginal cytology | Macroscopic examination plus histology on gross lesions<br>Collection of reproductive organs for possible histology<br>Quantitation of corpora lutea and implantation sites<br>Seminology (count, motility and morphology) |
| Embryo-fetal development | | Clinical signs and mortality<br>Body weights and changes<br>Feed intake | Macroscopic examination plus histology on gross lesions<br>Quantitation of corpora lutea and implantation sites<br>Fetal body weights<br>Fetal abnormalities |
| Pre- and postnatal development, including maternal function | | Clinical signs and mortality<br>Body weights and changes<br>Feed intake<br>Duration of pregnancy<br>Parturition | Macroscopic examination plus histology on gross lesions<br>Implantation<br>Abnormalities (including terata)<br>Live/dead offspring at birth<br>Pre- and postweaning survival and growth ($F_1$)<br>Physical development ($F_1$)<br>Sensory functions and reflexes ($F_1$)<br>Behavior ($F_1$) |

  - Distribution in normal and pregnant animals
  - Biotransformation
- Local tissue tolerance
- Environmental toxicity

In general, the registration process in the EU allows one to either apply to an overall medicines authority or to an individual national authority. Either of these steps is supposed to lead to mutual recognition by all the individual members.

***2.10.2.2 Japan*** In Japan, the Koseisho is the national regulatory body for new drugs. The standard $LD_{50}$ test is no longer a regulatory requirement for new medicines in the United States, the EU, or Japan. The Japanese guidelines were the first to be amended in accordance with this agreement, with the revised guidelines becoming effective in August 1993. The Japanese may still anticipate that single-dose (acute) toxicity studies should be conducted in at least two species, one rodent and one nonrodent (the rabbit is not accepted as a nonrodent). Both males and females should be included from at least one of the species selected: if the rodent, then a minimum of five per sex and if the nonrodent, at least two per sex. In nonrodents, both the oral and parenteral routes should be used, and normally the clinical route of administration should be employed. In nonrodents, only the intended route of administration needs to be employed; if the intended route of administration in humans is intravenous, then use of this route in both species is acceptable. An appropriate number of doses should be employed to obtain a complete toxicity profile and to establish any dose–response relationship. The severity, onset, progression, and reversibility of toxicity should be studied during a 14-day follow-up period, with all animals being necropsied. When macroscopic changes are noted, the tissue must be subjected to histological examination.

Chronic and subchronic toxicity studies are conducted to define the dose level, when given repeatedly, that cause toxicity and the dose level that does not lead to toxic findings. In Japan, such studies are referred to as repeated-dose toxicity studies. As with single-dose studies, at least two animal species should be used, one rodent and one nonrodent (rabbit not acceptable). In rodent studies, each group should consist of at least 10 males and 10 females; in nonrodent species, three of each sex are deemed adequate. Where interim examinations are planned, however, the numbers of animals employed should be increased accordingly. The planned route of administration in human subjects is normally explored. The duration of the study will be dictated by the planned duration of clinical use (Table 2.16).

At least three different dose groups should be included, with the goals of demonstrating an overtly toxic dose and a no-effect dose and establishing any dose–response relationship. The establishment of a nontoxic dose within the framework of these studies is more rigorously adhered to in Japan than elsewhere in the world. All surviving animals should also be necropsied, either at the completion of the study or during its extension recovery period, to assess reversal of toxicity and the possible appearance of delayed toxicity. Full histological examination is mandated on all nonrodent animals used in a chronic toxicity study; at a minimum, the highest-dose and control groups of rodents must be submitted to a full histological examination.

While the value of repeated-dose testing beyond 6 months has been questioned (Lumley et al., 1992), such testing is a regulatory requirement for a number of agencies, including the US FDA and the Koseisho. In Japan, repeated-dose testing for 12 months is required only for new medicines expected to be administered to humans for periods in excess of 6 months (Yakuji Nippo, 1994). At the first ICH held in Brussels, the consensus was that 12-month toxicity studies in rodents could be reduced to 6 months where carcinogenicity studies are required. While not yet adopted in the Japanese guidelines, 6-month repeated-dose toxicity studies have been accepted by the agencies of all three regions. Japan—like the EU—accepts a 6-month duration if accompanied by a carcinogenicity study. The United States still requires a 9-month nonrodent study.

**TABLE 2.16 Required Duration of Dosing in Nonclinical Study to Support Clinical Dosing**

| Duration of Dosing in Toxicity Study (months) | Duration of Human Exposure |
|---|---|
| 1 | Single dose or repeated dosage not exceeding 1 week |
| 3 | Repeated dosing exceeding 1 week and to a maximum of 4 weeks |
| 6 | Repeated dosing exceeding 4 weeks and to a maximum of 6 months |
| 12[a] | Repeated dosing exceeding 6 months or where this is deemed to be appropriate |

*Source*: New Drugs Division Notification No. 43, June 1992. CDER and CBER (2014), ICH (1997).

[a]Where carcinogenicity studies are to be conducted, the Koseisho had agreed to forego chronic dosage beyond 6 months.

With regard to reproductive toxicology, as a consequence of the first ICH, the United States, the EU, and Japan agreed to recommend mutual recognition of their respective current guidelines. A tripartite harmonized guideline on reproductive toxicology has achieved ICH step 4 status and should be incorporated into the local regulations of all three regions soon. This agreement represents a very significant achievement that should eliminate many obstacles to drug registration.

*Preclinical Male Fertility Studies* Before conducting a single-dose male volunteer study in Japan, it is usually necessary to have completed a preclinical male fertility study (segment 1) that has an in-life phase of 10 or more weeks (i.e., 10 weeks of dosing, plus follow-up). Although government guidelines do not require this study to be completed before phase I trials begin, the responsible institutional review board, or the investigator usually imposes this condition. Japanese regulatory authorities are aware that the segment 1 male fertility study is of poor predictive value. The rat, which is used in this study, produces a marked excess of sperm. Many scientists therefore believe that the test is less sensitive than the evaluation of testicular weight and histology that constitute part of the routine toxicology assessment

*Female Reproductive Studies* Before entering a female into a clinical study, it is necessary to have completed the entire reproductive toxicology program, which consists of the following studies:

- Segment 1: Fertility studies in the rat or mouse species used in the segment 2 program
- Segment 2: Teratology studies in the rat or mouse and the rabbit
- Segment 3: Late gestation and lactation studies in a species used in the segment 2 studies

Such studies usually take approximately 2 years. Although the US regulations state the need for completion of segments 1 and 2 and the demonstration of efficacy in male patients, where appropriate, before entering females into a clinical program, the current trend in the United States is toward relaxation of the requirements to encourage investigation of the drug both earlier and in a larger number of females during product development. Growing pressure for the earlier inclusion of women in drug testing may encourage selection of this issue as a future ICH topic. The trend in the United

States and the EU toward including women earlier in the critical program has not yet been embraced in Japan, however.

The three tests required in Japan for genotoxicity evaluation are a bacterial gene mutation test, *in vitro* cytogenetics, and *in vivo* tests for genetic damage. The Japanese regulations state these tests to be the minimum requirement and encourage additional tests. Currently, Japanese guidelines do not require a mammalian cell gene mutation assay. Harmonization will likely be achieved by the Koseisho recommending all four tests, which will match requirements in the United States and the EU; at present, this topic is at step 1 in the ICH harmonization process. The mutagenicity studies should be completed before the commencement of phase II clinical studies.

Guidelines presented at the second ICH are likely to alter the preclinical requirements for registration in Japan; they cover toxicokinetics and when to conduct repeated-dose tissue distribution studies. The former document may improve the ability of animal toxicology studies to predict possible adverse events in humans; currently, there are not toxicokinetic requirements in Japan, and their relevance is questioned by many there. Although there is general agreement on the registration requirement for single-dose tissue distribution studies, implementation of the repeated-dose study requirement has been inconsistent across the three ICH parties.

### 2.10.3 Safety Pharmacology

Japan was the first major country to required extensive pharmacological profiling on all new pharmaceutical agents as part of the safety assessment profile. Prior to commencement of initial clinical studies, the drug's pharmacology must be characterized in animal models. In the United States and Europe, these studies have been collectively called safety pharmacology studies. For a good general review of the issues surrounding safety pharmacology, the reader is referred to Hite (1997). The Japanese guidelines for such characterizations were published in 1991. They include:

- Effects on general activity and behavior
- Effects on the CNS
- Effects on the autonomic nervous system and smooth muscle
- Effects on the respiratory and cardiovascular systems
- Effects on the digestive system
- Effects on water and electrolyte metabolism
- Other important pharmacological effects

*Source*: New Drugs Division Notification No. 4, January 1991.

In the United States, pharmacological studies in demonstration of efficacy have always been required, but specific safety pharmacological studies have never been required. Special situational or mechanistic data would be requested on a case-by-case basis. This is a situation that is changing. In the United States the activities of the Safety Pharmacology Discussion Group, for example, have helped bring attention to the utility and issues surrounding safety pharmacology data. In 1999 and 2000, the major toxicological and pharmacological societal meetings had symposia on safety pharmacological testing. Many major US pharmaceutical companies are in the process of implementing programs in safety pharmacology. The issue has been taken up by ICH and the draft guideline is currently at the initial stages of review. This initial draft (Guideline S7) includes core tests in the assessment of CNS, cardiovascular, and respiratory function. Studies will be expected to be performed under GLP guidelines.

**TABLE 2.17 Composition of the Common Technical Document (ICH Format)**

| Module |
|---|
| 1 Regional administrative information |
| 2 Quality overall summary |
| Nonclinical overview |
| Nonclinical summary |
| Clinical overview |
| Clinical summary |
| 3 Quality data |
| 4 Nonclinical study reports |
| 5 Clinical study reports |

Even with harmonization as per ICH, there remain significant variations over the length of the entire process that takes a drug through to market (Hirako et al., 2007; Gad, 2012; Brock et al., 2013). These require guidance from a knowledgeable team of experts over the course of the process. This is especially true for emerging markets such as China (Deng and Kaitin, 2004). But the promulgation and near complete acceptance of a single format (the Common Technical Document—CTD) for worldwide regulatory submissions (see Table 2.17 for an outline of components) has been a huge step for global harmonization.

## 2.11 COMBINATION PRODUCTS

Recent years have seen a vast increase in the number of new therapeutic products which are not purely drug, device, or biologic, but rather a combination of two or more of these. This leads to a problem of deciding which of the three centers shall have ultimate jurisdiction.

The Center for Devices and Radiological Health (CDRH) is designated the center for major policy development and for the promulgation and interpretation of procedural regulations for medical devices under the Act. The CDRH regulates all medical devices inclusive of radiation-related device that are not assigned categorically or specifically to

CDER. In addition, the CDRH will independently administer the following activities (references to "Sections" are the provisions of the Act):

A. Small business assistance programs under Section 10 of the amendments (See PL 94-295). Both CDER and CDRH will identify any unique problems relating to medical device regulation for small business.
B. Registration and listing under Section 510 including some CDER-administered device applications. CDER will receive printouts and other assistance, as requested.
C. Color additives under Section 706, with review by CDER, as appropriate.
D. GMPs Advisory Committee. Under Section 520(f) (3), CDER will regularly receive notices of all meetings, with participation by CDER, as appropriate.
E. Medical Device Reporting. The manufacturers, distributors, importers, and users of all devices, including those regulated by CDER, shall report to CDRH under Section 519 of the Act as required. The CDRH will provide monthly reports and special reports as needed to CDER for investigation and follow-up of those medical devices regulated by CDER.

### 2.11.1 Device Programs That CDER and CBRH Each Will Administer

Both CDER and CDRH will administer and, as appropriate, enforce the following activities for medical devices assigned to their respective centers (references to "Sections" are the provisions of the Act):

A. Surveillance and compliance actions involving general controls violations, such as misbranded or adulterated devices under Section 301, 501, and 502
B. Warning letters, seizures, injunctions, and prosecutions under Section 302, 303, and 304
C. Civil penalties under Section 303(f) and administrative restraint under Section 304(g)
D. Nonregulatory activities, such as educational programs directed at users, participation in voluntary standards organizations, etc.
E. Promulgation of performance standards and applications of special controls under Section 514
F. Premarket notification; investigational device exemptions including humanitarian exemptions; premarket approval; product development protocols; classification; device tracking; petitions for reclassification; postmarket surveillance under Sections 510(k), 513, 515, 519, 520(g) & (m), and 522; and the advisory committees necessary to support these activities
G. Banned devices under Section 516
H. FDA-requested and firm-initiated recalls whether under Section 518 or another authority and other Section 518 remedies such as recall orders
I. Exemptions, variances, and applications of CGMP regulations under Section 520(f)
J. Government-wide quality assurance program
K. Requests for export approval under Sections 801(e) and 802

### 2.11.2 Coordination

The centers will coordinate their activities in order to assure that manufacturers do not have to independently secure authorization to market their product from both centers unless this requirement is specified in Section VII.

### 2.11.3 Submissions

Submissions should be made to the appropriate center, as specified herein, at the addresses provided as follows:

Address update:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (Room #2–14)
12420 Parklawn Drive
Rockville, MD 20852
or
Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center (HFZ-401)
1390 Piccard Drive
Rockville, MD 20850

For submissions involving medical devices and/or drugs that are not clearly addressed in this agreement, sponsors are referred to the product jurisdiction regulations (21 CFR Part 3). These regulations have been promulgated to facilitate the determination of regulatory jurisdiction but do not exclude the possibility for a collaborative review between the centers.

***2.11.3.1 Center Jurisdiction*** The following subsections provide details concerning status, market approval authority, special label/regulatory considerations, investigational options, and intercenter consultations for the categories of products specified. Section VII provides the general criteria that CDRH and CDER will apply in reaching decisions as to which center will regulate a product.

A. 1. a. Device with primary purpose of delivering or aiding in the delivery of a drug that is distributed without a drug (i.e., unfilled)

**Examples**

Devices that calculate drug dosages

Drug delivery pump and/or catheter infusion pump for implantation

Iontophoresis device

Medical or surgical kit (e.g., tray) with reference in instructions for use with specific drug (e.g., local anesthetic)

Nebulizer

Small particle aerosol generator (SPAG) for administering drug to ventilated patient

Splitter block for mixing nitrous oxide and oxygen

Syringe, jet injector, and storage and dispensing equipment

*Status* Device and drug, as separate entities.

*Market approval authority* CDRH and CDER, respectively, unless the intended use of the two products, through labeling, creates a combination product.

*Special label/regulatory considerations* The following specific procedures will apply depending on the status of the drug delivery device and drugs that will be delivered with the device:

(i) It may be determined during the design or conduct of clinical trials for a new drug that it is not possible to develop adequate performance specifications data on those characteristics of the device that are required for the safe and effective use of the drug. If this is the case, then drug labeling cannot be written to contain information that makes it possible for the user to substitute a generic, marketed device for the device used during developments to use with the marketed drug. In these situations, CDER will be the lead center for regulation of the device under the device authorities.

(ii) For a device intended for use with a category of drugs that are on the market, CDRH will be the lead center for regulation for the device under the device authorities. The effects of the device use on drug stability must be addressed in the device submission, when relevant. An additional showing of clinical effectiveness of the drug when delivered by the specific device will generally not be required. The device and drug labeling must be mutually conforming with respect to indication, general mode of delivery (e.g., topical, IV), and drug dosage/schedule equivalents.

(iii) For a drug delivery device and drug that are developed for marketing to be used together as a system, a lead center will be designated to be the contact point with the manufacturer(s). If a drug has been developed and marketed and the development and studying of device technology predominate, the principal mode of action will be deemed to be that of the device, and CDRH would have the lead. If a device has been developed and marketed and the development and studying of drug predominate, then, correspondingly, CDER would have the lead. If neither the drug nor the device is on the market, the lead center will be determined on a case-by-case basis.

*Investigation options* IDE or IND, as appropriate.

*Intercenter consultation* CDER, when lead center, will consult with CDRH if CDER determines that a specific device is required as part of the NDA process. CDRH as lead center will consult with CDER if the device is intended for use with a marketed drug and the device creates a significant change in the intended use, mode of delivery (e.g., topical, IV), or dose/schedule of the drug.

H. Device with primary purpose of delivering or aiding in the delivery of a drug and distributed containing a drug (i.e., "prefilled delivery system")

**Examples**

Nebulizer

Oxygen tank for therapy and OTC emergency use

Prefilled syringe

Transdermal patch

*Status* Combination product.

*Market approval authority* CDER using drug authorities and device authorities, as necessary.

*Special label/regulatory considerations* None.

*Investigation options* IND.

*Intercenter consultations* Optional.

2. Device incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function

**Examples**

Bone cement containing antimicrobial agent

Cardiac pacemaker lead with steroid-coated tip

Condom, diaphragm, or cervical cap with contraceptive or antimicrobial agent (including virucidal) agent

Dental device with fluoride

Dental wood wedge with hemostatic agent

Percutaneous cuff (e.g., for a catheter or orthopedic pin) coated/impregnated with antimicrobial agent

Skin closure or bandage with antimicrobial agent

Surgical or barrier drape with antimicrobial agent

Tissue graft with antimicrobial or other drug agent

Urinary and vascular catheter coated/impregnated with antimicrobial agent

Wound dressing with antimicrobial agent

*Status* Combination product.

*Market approval authority* CDRH using device authorities.

*Special label/regulatory considerations* These products have a drug component that is present to augment the safety and/or efficacy of the device.

*Investigation options* IDE.

*Intercenter consultation* Required if a drug or the chemical form of the drug has not been legally marketed in the United States as a human drug for the intended effect.

3. Drug incorporating a device component with the combination product having the primary intended purpose of fulfilling a drug function

**Examples**

Skin-prep pads with antimicrobial agent

Surgical scrub brush with antimicrobial agent

*Status* Combination product.

*Market approval authority* CDER using drug authorities and, as necessary, device authorities.

*Special label/regulatory considerations* Marketing of such a device requires a submission of an NDA with safety and efficacy data on the drug component or it meets monograph specifications as generally recognized as safe (GRAS) and generally recognized as effective (GRAE). Drug requirements, for example, CGMPs, registration and listing, and experience reporting, apply to products.

*Investigation options* IND.

*Intercenter consultation* Optional.

4. a. Device used in the production of a drug either to deliver directly to a patient or for the use in the producing medical facility (excluding use in a registered drug manufacturing facility)

**Examples**

Oxygen concentrators (home or hospital)

Oxygen generator (chemical)

Ozone generator

*Status* Device

*Market approval authority* CDER, applying both drug and device authorities.

*Special label/regulatory consideration* May also require and NDA if the drug produced is a new drug. Device requirements (e.g., CGMPs, registration and listing, experience reporting) will apply to products.

*Investigation options* IDA, or NDA, as appropriate,

*Intercenter consultation* Optional.

b. Drug/device combination product intended to process a drug into a finished package form

**Examples**

Device that uses drug concentrates to prepare large-volume parenterals

Oxygen concentrator (hospital) output used to fill oxygen tanks for use within that medical facility

*Status* Combination product.

*Market approval authority* CDER, applying both drug and device authorities.

*Special label/regulatory considerations* Respective drug and device requirements (e.g., CGMPs, registration and listing, experience reporting) will apply.

*Investigation options* IDE or NDA, as appropriate.

*Intercenter consultation* Optional, but will be routinely obtained.

B. 1. Device used concomitantly with a drug to directly activate or to augment drug effectiveness

**Examples**

Biliary lithotriptor used in conjunction with dissolution agent

Cancer hyperthermia used in conjunction with chemotherapy

Current generator used in conjunction with an implanted silver electrode (drug) that produces silver ions for an antimicrobial purpose

Materials for blocking blood flow temporarily to restrict chemotherapy drug to the intended site of action

UV and/or laser activation of oxsoralen for psoriasis or cutaneous T-cell lymphoma

*Status* Device and drug, as separate entities.

*Market approval authority* CDRH and CDER, respectively.

*Special label/regulatory considerations* The device and drug labeling must be mutually conforming with respect to indications, general mode of delivery (e.g., topical, IV), and drug dosage/schedule equivalence. A lead center will be designated to be the contact point with the manufacturer. If a drug has been developed and approved for another use and the development and studying of device technology predominate, then CDRH would have lead. If a device has been developed and marketed for another use and the development

and studying of drug action predominate, then CDER would have lead. If neither the drug nor the device is on the market, the lead center will be determined on a case-by-case basis. If the labeling of the drug and device creates a combination product, as defined in the combination product regulations, then the designation of the lead center for both applications will be based upon a determination of the product's primary mode of action.

*Investigation options* IDE or IND, as appropriate.

*Intercenter consultations* Required.

2. Device kits labeled for use with drugs that include both device(s) and drug(s) as separate entities in one package with the overall primary intended purpose of the kit fulfilling a device function

**Examples**

Medical or surgical kit (e.g., tray) with drug component

*Status* Combination product.

*Market approval authority* CDRH, using device authorities, is responsible for the kit if the manufacturer is repackaging a market drug. Responsibility for overall packaging resides with CDRH. CDER will be consulted as necessary on the use of drug authorities for the repackaged drug component.

*Special label/regulatory consideration* Device requirements (e.g., CGMPs, registration and listing, experience reporting) apply to kits. Device manufacturers must assure that manufacturing steps do not adversely affect drug components of the kit. If the manufacturing steps do affect the marketed drug (e.g., the kit is sterilized by irradiation), ANDA or NDA would also be required with CDRH as lead center.

*Investigation options* IDA or IND, as appropriate.

*Intercenter consultation* Optional if ANDA or NDA not required.

C. Liquids, gases, or solids intended for use as devices (e.g., implanted, or components, parts, or accessories to devices)

**Examples**

Dye for tissues used in conjunction with laser surgery to enhance absorption of laser light in target tissue

Gas mixtures for pulmonary function testing devices

Gases used to provide "physical effects"

Hemodialysis fluids

Hemostatic devices and dressings

Injectable silicon, collagen, and Teflon

Liquids functioning through physical action applied to the body to cool or freeze tissues for therapeutic purposes

Liquids intended to inflate, flush, or moisten (lubricate) indwelling device (in or on the body)

Lubricants and lubricating jellies

Ophthalmic solutions for contact lenses

Organ/tissue transport and/or perfusion fluid with antimicrobial or other drug agent, that is, preservation solutions

Powders for lubricating surgical gloves

Sodium hyaluronate or hyaluronic acid for use as a surgical aid

Solution for use with dental "chemical drill"

Spray on dressings not containing a drug component

*Status* Device

*Market approval authority* CDRH

*Special label/regulatory considerations* None

*Investigation options* IDE

*Intercenter consultation* Required if the device has direct contact with the body and the drug or the chemical form of the drug has not been legally marketed as a human drug

D. Products regulated as drugs

**Examples**

Irrigation solutions

Purified water or saline in prefilled nebulizers for use in inhalation therapy

Skin protectants (intended for use on intact skin)

Sun screens

Topical/internal analgesic-antipyretic

*Status* Drug

*Market approval authority* CDER

*Special label/regulatory considerations* None

*Investigation options* IND

*Intercenter consultations* Optional

E. Ad Hoc Jurisdictional Decisions.

| Examples | Status | Center |
|---|---|---|
| Motility marker constructed of radiopaque plastic | Device | CDRH |
| Brachytherapy capsules, needles, etc., that are radioactive and may be removed from the body after radiation therapy has been administered | Device | CDRH |
| Skin markers | Device | CDRH |

*Status* Device or drug

*Market approval authority* CDRH or CDER as indicated

*Special label/regulatory considerations* None

*Investigation options* IDE or IND, as appropriate

*Intercenter consultation* Required to assure agreement on drug/device status

***2.11.3.2 General Criteria Affecting Drug/Device Determination*** The following represent the general criteria that will apply in making device/drug determinations:

A. Device criteria

1. A liquid, powder, or other similar formulation intended only to serve as a component, part, or accessory to a device with a primary mode of action that is physical in nature will be regulated as a device by CDRH.
2. A product that has the physical attributes described in 201(h) (e.g., instrument, apparatus) of the Act and does not achieve its primary intended purpose through chemical action within or on the body, or by being metabolized, will be regulated as a device by CDRH.
3. The phrase "within or on the body" as used in 201(h) of the Act does not include extracorporeal systems or the solutions used in conjunction with such equipment. Such equipment and solutions will be regulated as devices by CDRH.
4. An implant, including an injectable material, placed in the body for primarily a structural purpose even though such an implant may be absorbed or metabolized by the body after it has achieved its primary purpose will be regulated as a device by CDRH.
5. A device containing a drug substance as a component with the primary purpose of the combination being to fulfill a device function is a combination product and will be regulated as a device by CDRH.
6. A device (e.g., machine or equipment) marketed to the user, pharmacy, or licensed practitioner that produces a drug will be regulated as a device or combination product by CDER. This does not include equipment marketed to a registered drug manufacturer.
7. A device whose labeling or promotional materials make reference to a specific drug or generic class of drugs unless it is prefilled with a drug ordinarily remains a device regulated by CDRH. It may, however, also be subject to the combination products regulation.

B. Drug criteria

1. A liquid, powder, tablet, or other similar formulation that achieves its primary intended purpose through chemical action within or on the body, or by being metabolized, unless it meets one of the specified device criteria, will as regulated as a drug by CDER.
2. A device that serves as a container for a drug or a device that is a drug delivery system attached to the drug container where the drug is present in the container is a combination product that will be regulated as a drug by CDER.
3. A device containing a drug substance as a component with the primary purpose of the combination product being to fulfill a drug purpose is a combination product and will be regulated as a drug by CDER.
4. A drug whose labeling or promotional materials makes reference to a specific device or generic class of devices ordinarily remains a drug regulated by CDER. It may, however, also be subject to the combination products regulation.

## 2.12 CONCLUSIONS

In summary, we have touched upon the regulations that currently control the types of preclinical toxicity testing done on potential human pharmaceuticals and medical device products. We have reviewed the history, the law, the regulations themselves, the guidelines, and common practices employed to meet regulatory standards. Types of toxicity testing were discussed, as were the special cases pertaining to, for example, biotechnology products.

## REFERENCES

Alder S, Zbinden G. (Eds.) (1988) *National and International Drug Safety Guidelines*. M.T.C. Verlag, Zollikon.

Anderson OE. (1958) *The Health of a Nation: Harvey W. Wiley and the Fight for Pure Food*. University of Chicago Press, Chicago, IL.

Anonymous. (1991) Points to consider in human somatic cell therapy and gene therapy. *Hum. Gene Ther.* 2(3):251–265.

Anonymous. (1992/2015) FDA's policy statement for the development of new stereoisomeric drugs. *Chirality*. 4(5):338–340.

Anonymous. (1996) "Well-Characterized" biologics would be regulated under FD&C act by Kassebaum FDA reform bill. *F-D-C Rep. (Pink Sheets)*. 58:11–12.

Anonymous (2013) *Orphan Drug Regulations*. 21 CFR Part 316. 57 FR 62085, December 29, 1992, as amended at 78 FR 35133, June 12, 2013.

Barton BL. (1998) International conference on harmonization—good clinical practices update. *Drug Inf. J.* 32(4):1143–1147.

Berliner VR. (1974) U.S. Food and Drug Administration requirements for toxicity testing of contraceptive products. *Acta Endocrinol. Suppl. (Copenhagen)*. 185:240–265.

Blakeslee D. (1998) *Thalidomide: A Background Briefing*. JAMA HIV/AIDS Information Center. Centers for Disease Control (CDC), Atlanta, GA.

Brock WJ, Hastings KL, McGown KM. (2013) *Nonclinical Safety Assessment: A Guide to International Pharmaceutical Regulations*. John Wiley & Sons, Inc., Hoboken, NJ.

Brusick D. (1987) *Principles of Genetic Toxicology*, 2nd Ed. Plenum Press, New York.

Burns J. (1983) Overview of safety regulations governing food, drug and cosmetics. In: *The United States in Safety and Evaluation and Regulation of Chemicals 3: Interface between Law and Science* (Homberger F, Ed.). Karger, New York.

CDER (1989) *Guideline for the Study of Drugs Likely to be Used in the Elderly*. CDER, Rockville, MD.

CDER (1998) *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act*. CDER, Rockville, MD. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078754.pdf (accessed November 11, 2015).

CDER and CBER (1995) *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*. CDER and CBER, Rockville, MD. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071597.pdf (accessed November 16, 2015).

CDER and CBER (2001) *Content and Format for Geriatric Labeling*. CDER and CBER, Rockville, MD. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075062.pdf (accessed November 11, 2015).

CDER and CBER (2014) *Expedited Programs for Serious Conditions—Drugs and Biologics*. CDER and CBER, Silver Spring, MD. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf (accessed November 16, 2015).

Daniels JM, Nestmann ER, Kerr AI. (1997) Development of stereoisomeric (chiral) drugs: a brief review of scientific and regulatory considerations. *Drug Inf. J.* 31(3):639–646.

De Camp WH. (1989) The FDA perspective on the development of stereoisomers. *Chirality*. 1(1):2–6.

DeGeorge JJ, Ahn C-H, Andrews PA, Brower ME, Giorgio DW, Goheer MA, Lee-Ham DY, McGuinn WD, Schmidt W, Sun CJ, Tripathi SC. (1998) Regulatory considerations for preclinical development of anticancer drugs. *Cancer Chemother. Pharmacol.* 41(3):173–185.

Deng R, Kaitin KI. (2004) The regulation and approval of new drugs in China. *Drug Inf. J.* 38(1):29–39.

DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. (1991) Cost of innovation in the pharmaceutical industry. *J. Health Econ.* 10(2):107–142.

DiMasi JA, Seibring MA, Lasagna L. (1994) New drug development in the United States from 1963-1992. *Clin. Pharmacol. Ther.* 55(6):609–622.

Ember LR. (2001) Raising the bar for quality drugs. *Chem. Eng. News*. 79(12):26.

FDA. (1987) *Environmental Assessment Technical Assistance Handbook*. National Technical Information Service, Washington, DC.

FDA (1988) *Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses*. CFR 21 Parts 312 and 314, Rockville, MD.

FDA. (1993) *Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals*. FDA, Washington, DC.

FDA (1997) *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*. Center for Biologics Evaluation and Research, Rockville, MD. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/UCM153182.pdf (accessed December 4, 2015).

FDA (2015) *Good Laboratory Practice for Nonclinical Laboratory Studies*, Silver Spring, MD. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=58 (accessed November 16, 2015).

Fung M, Thornton A, Mybeck K, Wu JH-H, Hornbuckle K, Muniz E. (2001) Evaluation of the characteristics of safety withdrawal of prescription drugs from worldwide pharmaceutical markets—1960–1999. *Drug Inf. J.* 35(1):293–317.

Gad SC. (2012) *Safety Pharmacology in Pharmaceutical Development: Approval and Post Marketing Surveillance*, 2nd Ed. CRC Press, Boca Raton, FL.

Goldenthal EI. (1968) Current views on safety evaluation of drugs. *FDA Pap.* 2(4):13–18.

Grabowski HG, Vernon JM. (1983) *The Regulation of Pharmaceuticals: Balancing the Benefits and Risks*. American Enterprise Institute for Public Policy Research, Washington, DC.

Greishaber C. (1991) Prediction of human toxicity of new antineoplastic drugs from studies in animals. In: *The Toxicity of Anticancer Drugs* (Powis G and Hacker M, Eds.). Pergamon Press, New York, pp. 10–24.

Haffner ME. (1998) Orphan drug development—international program and study design issues. *Ther. Innov. Regul. Sci.* 32(1):93–99.

Hart C. (1999) Getting past the politics and paperwork of pediatric drug studies. *Mod. Drug Discovery*. 2:15–16.

Hayes TJ, Ryffel B. (1997) Symposium-in-writing: safety considerations of recombinant protein therapy; Introductory comments. *Clin. Immunol. Immunother.* 83:1–4.

Hirako M, McAuslane N, Salek S, Anderson C, Walker S. (2007) A comparison of the drug review process at five international regulatory agencies. *Drug Inf. J.* 41(3):291–308.

Hite M. (1997) Safety pharmacology approaches. *Int. J. Toxicol.* 16(1):23–31.

Holtzman DC. (1993) European biotech firms invest in US facilities. *Bioworld Today*.

Hutt PB. (1983a) Investigations and reports respecting FDA regulations of new drugs (Part I). *Clin. Pharmacol. Ther.* 33:537–548.

Hutt PB. (1983b) Investigations and reports respecting FDA regulations of new drugs (Part II). *Clin. Pharmacol. Ther.* 33:174–187.

Hutt PB. (1987) Progress in new drug regulation. *Clin. Res. Pract. Drug Regul. Aff.* 5(5–6):307–318.

ICH. (1997) *International Conference on Harmonization Safety Steps 4/5 Documents*. Interpharm Press, Buffalo Grove, IL.

ICH (2009) *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)*. International Council for Harmonisation, Geneva, Switzerland. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf (accessed April 28, 2016).

Jackson CO. (1970) *Food and Drug Legislation and the New Deal*. Princeton University Press, Princeton, NJ.

Kessler DA, Siegel JP, Noguchi PD, Zoon KC, Feiden KL, Woodcock J. (1993) Regulation of somatic-cell therapy and gene therapy by the Food and Drug Administration. *N. Engl. J. Med.* 329(16):1169–1173.

Leibert MA. (1996) Addendum to points to consider in human somatic cell and gene therapy (1991). *Hum. Gene Ther.* 7:1181–1190.

Lumley CE, Parkinson C, Walker S. (1992) An international appraisal of the minimum duration of chronic animal toxicity studies. *Hum. Exp. Toxicol.* 11(3):155–162.

Manson JM. (1994) Testing of pharmaceutical agents for reproductive toxicity. In: *Developmental Toxicology* (Kimmel CA and Beulke-Sam J, Eds.). Raven Press, New York, pp. 379–402.

Marwick C. (1998) Implementing the FDA modernization act. *JAMA*. 279(11):815–816.

Merrill RA. (1994) Regulation of drugs and devices: an evolution. *Health Aff.* 13(3):47–69.

Ohno Y. (1999) Harmonization of the timing of non-clinical tests in relation to the conduct of clinical trials. *J. Control. Release*. 62(1–2):57–63.

Pendergast W. (1984) Biological Drug Regulation. In: *75th Anniversary Commemorative Volume of Food and Drug Law* (Institute FaDL, Ed.). Food and Drug Law Institute, Washington, DC, pp. 293–305.

PhRMA. (1998) *Annual Report of the Pharmaceutical Research and Manufacturer Association (Priority #2: Improved FDA Regulation of Drug Development)*. PhRMA, Washington, DC.

Pilot LR, Waldmann DR. (1998) Food and Drug Administration Modernization Act of 1997: medical device provisions. *Food Drug Law J.* 53:267–295.

Ryffel B. (1996) Unanticipated human toxicology of recombinant proteins. *Arch. Toxicol. Suppl.* 18:333–341.

Shacter E, DeSantis PL. (1998) Labeling of drug and biologic products for pediatric use. *Drug Inf. J.* 32:299–303.

Tambuyzer E. (2010) Rare diseases, orphan drugs and their regulation: questions and misconceptions. *Nat. Rev. Drug Discov.* 9(12):921–929.

Temin P. (1980) *Taking Your Medicine: Drug Regulation in the United States*. Harvard University Press, Cambridge, MA.

Tufts. (2014) *Cost to Develop and Win Marketing Approval of a New Drug is $2.6 Billion Press Release*. Tufts University Center for the Study of Drug Development, Boston, MA.

USP (2015) *United States Pharmacopeia XXXIX, National Formulary 34*. Available at: http://www.usp.org/usp-nf (accessed November 16, 2015).

Wu K-M, DeGeorge JG, Atrakchi A, Barry E, Bigger A, Chen C, Du T, Freed L, Geyer H, Goheer A, Jacobs A, Jean D, Rhee H, Osterberg R, Schmidt W, Farrelly JG. (2000) Regulatory science: a special update from the United States Food and Drug Administration; preclinical issues and status of investigation of botanical drug products in the United States. *Toxicol. Lett.* 111(3):199–202.

Yakuji Nippo. (1994) *Guidelines for Toxicity Study of Drugs Manual*. Yakuji Nippo, Tokyo.

## FURTHER READING

Beusing MA, McSweegan E. (1999) Submitting biologics applications to the Center for Biologics Evaluation and Research electronically. *Drug Inf. J.* 33(1):1–15.

Cadden S. (1999) *New Drug Approval in Canada*. Parexel, Waltham, MA.

CDRH (1990) *Premarket Notification, 510(k): Regulatory Requirements for Medical Devices*. CDRH, Rockville, MD. Available at: http://babel.hathitrust.org/cgi/pt?id=mdp.39015041531420;view=1up;seq=1;size=150 (accessed March 18, 2015).

Currie WJ. (1995) *New Drug Approval in Japan*. Parexel, Waltham, MA.

DiMasi JA, Reichert JM, Feldman L, Malins A. (2013) Clinical approval success rates for investigational cancer drugs. *Clin. Pharmacol. Ther.* 94(3):107–142.

Evers PT. (1995) *New Drug Approval in the European Union*. Parexel, Waltham, MA.

FDA. (1973) *FDA Introduction to Total Drug Quality*. U.S. Government Printing Office, Washington, DC.

FDA. (1985) *Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology*. Office of Biologics Research and Review, Bethesda, MD.

FDA. (1998) *Guidance for Human Somatic Cell Therapy and Gene Therapy*. CBER, Rockville, MD.

Gad SC. (2009) *Drug Safety Evaluation*, 2nd Ed. John Wiley & Sons, Inc., Hoboken, NJ.

Gad SC. (2011) *Safety Evaluation of Pharmaceuticals and Medical Devices: International Regulatory Guidelines*. Springer US, New York.

Guarino RA. (2009) *New Drug Approval Process*. CRC Press, Boca Raton, FL.

Hess G. (1999) FDA accelerates it's approval of new drugs. *Chem. Mark. Newsl.* 255:21.

Mantus D, Pisano DJ. (2014) *FDA Regulatory Affairs*. CRC Press, Boca Raton, FL.

PhRMA. (2015) *2015 Biopharmaceutical Research Industry Profile*. Pharmaceutical Research and Manufacturers of America, Washington, DC.

Ryffel B. (1997) Safety of human recombinant proteins. *Biomed. Environ. Sci.* 10(1):65–72.

Wessinger J. (1989) Nonclinical pharmacologic and toxicologic considerations for evaluating biologic products. *Regul. Toxicol. Pharmacol.* 10(3):255–263.

Yakuji Nippo. (1993) *Drug Registration Requirements in Japan*. Yakuji Nippo, Tokyo.

Young F, Nightingale S, Mitchell W, Beaver L. (1989) The United States Drug Export Amendment Act of 1986: perspectives from the Food and Drug Administration. *Int. Dig. Health Legis.* 40:246–252.

# 3

# DATA MINING: SOURCES OF INFORMATION FOR CONSIDERATION IN STUDY AND PROGRAM DESIGN AND IN SAFETY EVALUATION

## 3.1 INTRODUCTION

The appropriate starting place for the safety assessment of any new chemical entity (NCE), particularly a potential new drug, is to first determine what is already known about the molecule, its structural and therapeutics or functional class analogs (pharmacological analogs being agents with assumed similar pharmacological mechanisms), and the disease one seeks to treat. Such a determination requires the fullest possible access and review of the available literature. Here we try to provide a fundamental overview of the current range of approaches to gathering such data (Table 3.1). In using this information, one must keep in mind that there is both an initial requirement to build a data file or database and a continuing need to update such a database or files on a regular basis, serving as part of the project record. Updating a database requires not merely adding to what is already there but also discarding out-of-date (i.e., now known to be incorrect) information and reviewing the entire structure for connections and organization.

Such data is first used in selecting which possible compounds should be carried forward in development as a possible new drug (as illustrated in Figure 3.1 and explored in detail in Gad (2005)). A multitude of reasons for collecting and for uses of data should be recognized and considered.

### 3.1.1 Claims

Claims are what is said in labeling and advertising and may be either of a positive (therapeutic or beneficial) or negative (lack of an adverse effect) nature. The positive or efficacy claims are not usually the direct concern of the toxicologist though it must be kept in mind that such claims both must be proven and can easily exceed the limits of the statutory definition of a device, turning the product into a drug or combination product.

Negative claims such as "nonirritating" or "hypoallergenic" also must be proven and are generally the responsibility of the product safety professional to substantiate. There are special tests for such claims.

### 3.1.2 Time and Economies

The final factors of influence or arbitrator of test conduct and timing are the requirements of the marketplace, the resources of the organization, and the economic worth of the product.

Plans for filings with regulatory agencies and for market launches are typically set before actual testing (or final stage development) is undertaken, as the need to be in the marketplace within a certain time frame is critical. Such timing and economic issues are beyond the scope of this volume but must be considered.

### 3.1.3 Prior Knowledge

The appropriate starting place for the safety assessment of any NCE, particularly a potential new material for a medical device, is to first determine what is already known about the material and whether there are any close structural or pharmacological analogs (pharmacological analogs being agents with assumed similar pharmacological mechanisms). Such a determination requires complete access to the available literature. In using this information, one must keep in mind that there is both an initial requirement to build a data file or database and a need to update

*Drug Safety Evaluation*, Third Edition. Shayne Cox Gad.

**TABLE 3.1 Sources of Prior Art**

| |
|---|
| Internet |
| FDA: Inactive ingredients for currently marketed drug products, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm |
| Proprietary databases |
| MEDLINE/TOXLINE/journals |
| Book (monographs and edited) |
| Personal network/meetings |
| Obscure databases |

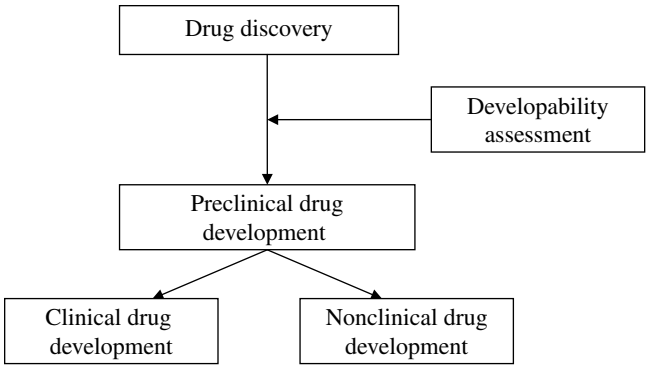



**FIGURE 3.1** Prior art in assessing pharmaceutical developability.

such a store on a regular basis. Updating a database requires not merely adding to what is already there but also discarding out-of-date (i.e., now known to be incorrect) information and reviewing the entire structure for connections and organization.

The first step in any new literature review is to obtain as much of the following information as possible:

- Correct chemical identity including molecular formula, Chemical Abstracts Service (CAS) Registry Number, common synonyms, trade names, and a structural diagram. Gosselin et al. (1984), Ash and Ash (2007, 2008), and the USP (2015) (and ongoing) are excellent sources of information on existing commercial products and their components and uses. Limited by being print sources but still relevant.
- Chemical composition (if a mixture) and major impurities.
- Production and use information.
- Chemical and physical properties (physical state, vapor pressure, pH, solubility, chemical reactivity, etc.).
- Any structurally related chemical substances that are already on the market or in production.
- Known or presumed pharmacological properties.

Collection of the previous information is not only important for hazard assessment (high vapor pressure would indicate high inhalation potential, just as high and low pH would indicate high irritation potential), but the prior identification of all intended use and exposure patterns may provide leads to alternative information sources; for example, drugs to be used as antineoplastics or antibiotics may already have extensive toxicology data obtainable from government or private sources. A great deal of the existing toxicity information (particularly information on acute toxicity) is not available in the published or electronic literature because of concerns about the proprietary nature of this information and the widespread opinion that it does not have enough intrinsic scholarly value to merit publication. This unavailability is unfortunate, as it leads to a lot of replication of effort and expenditure of resources that could be better used elsewhere. It also means that an experienced toxicologist must use an informal search of the unpublished literature and the knowledge of their colleagues as a supplement to searches of the published and electronic literature.

There are now numerous published texts that should be considered for use in literature-reviewing activities. An alphabetic listing of 36 of the more commonly used hard copy sources for safety assessment data is presented in Table 3.2 and included in the reference section of this chapter. Obviously, this is not a complete listing and consists of only the general multipurpose texts that have a wider range of applicability for toxicology. Texts dealing with specialized classes of agents (e.g., disinfectants, excipients, and pharmaceutical salts) or with specific target organ toxicity (neurotoxins and teratogens) are generally beyond the scope of this text. Parker (1988) should be consulted for details on the use of these texts. Wexler (2009), Parker (1988), and Sidhu et al. (1989) should be consulted for more extensive listings of the literature and computerized databases. Such sources can be of direct (free) Internet sources (where one must beware of garbage in, garbage out (GIGO)), commercial databases, and package products, to mention just the major categories. Appendix C provides addresses for major free Internet sources.

### 3.1.4 Miscellaneous Reference Sources

There are some excellent published information sources covering some specific classes of chemicals, for example, heavy metals, plastics, resins, or petroleum hydrocarbons. The National Academy of Science series *Medical and Biologic Effects of Environment Pollutants* covers 10–15 substances considered to be environmental pollutants. *Scientific American Medicine* presents a current (and consistently updated) summary of knowledge of diseases and treatments. *CRC Critical Reviews in Toxicology* is a well-known scientific journal that over the years has compiled over 26 volumes of extensive literature reviews of a wide variety of chemical substances. A photocopy of this journal's topical index will prevent one from overlooking information that may be contained in this important source. Trade organizations

**TABLE 3.2 Key Safety Assessment Reference Texts**


Abraham DJ (Ed.) (2010) *Burger's Medicinal Chemistry and Drug Discovery*, 7th Ed. John Wiley & Sons, New York.

American Conference of Governmental Industrial Hygienists (ACGIH) (2012) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 7th Ed. ACGIH, Cincinnati, OH.

Ash M and Ash I. (2007) Pharmaceutical additives. In: *Electronic Handbook* 3rd Ed. Gower, Brookfield, VT.

Ash M and Ash I. (2008) Food additives. In: *Electronic Handbook* 3rd Ed. Gower, Brookfield, VT.

Bingham E and Cohrssen B. (Eds.) (2012) *Patty's Toxicology*, 6th Ed. John Wiley & Sons, New York.

Brayfield A. (Ed.) (2014) *Martindale: The Complete Drug Reference*. Pharmaceutical Press, London.

Center for Disease Control (2016) *Registry of the Toxic Effects of Chemical Substances (RTECS)*. National Institute for Occupational Safety and Health.

Cronin E. (1980) *Contact Dermatitis*. Churchill Livingston, Edinburgh.

Dart RC. (2004) *Medical Toxicology*, 3rd Ed. Lippincott Williams, Wilkins, PA.

Deichmann W and Gerard H. (1996) *Toxicology of Drugs and Chemicals*. Academic Press, New York.

Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, and Posey LM. (Eds.) (2014) *Pharmacotherapy: A Pathophysiologic Approach*, 9th Ed. McGraw-Hill, New York.

FDA (2015) *Inactive Ingredient Database*. Available at http://www.fda.gov/downloads/drugs/informationondrugs/UCM080154.zip (accessed January 12, 2016).

Ford MD. (Ed.) (2001) *Clinical Toxicology*. W.B. Saunders Company, Philadelphia.

Gad SC and Chengelis CP. (1998) *Acute Toxicology Testing*, 2nd Ed. Academic Press, San Diego, CA.

Gosselin RE, Smith RP, and Hodge HC. (Eds.) (1984) *Clinical Toxicology of Commercial Products*, 5th Ed. Williams & Wilkins, Baltimore, MD.

Grant WM. (1993) *Toxicology of the Eye*, 4th Ed. Charles C. Thomas, Springfield, IL.

Harbison RD, Bourgeois MM, and Johnson GT. (Eds.) (2015) *Hamilton and Hardy's Industrial Toxicology*, 6th Ed. John Wiley & Sons, Inc., Hoboken, NJ.

Klaassen CD. (Ed.) (2013) *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 7th Ed. McGraw-Hill, New York.

Lewis RJ. (Ed.) (1991) *Carcinogenically Active Chemicals: A Reference Guide*. Van Nostrand Reinhold, New York.

Lewis RJ. (2012) *Sax's Dangerous Properties of Industrial Materials*, 12th Ed. John Wiley & Sons, Inc., Hoboken, NJ.

National Toxicology Program (NTP). (2000) *Nineteenth Annual Report on Carcinogens*. PB 85-134633. Department of Health and Human Services, Washington, DC.

O'Neil MJ. (2013) *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 15th Ed. Royal Society of Chemistry, Whitehouse Station, NJ.

PDR. (2015) *Physician's Desk Reference*, 69th Ed. PDR Network, Montvale, NJ.

Pohanish RP. (Ed.) (2011) *Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens*, 6th Ed. Elsevier, Oxford.

Proctor NH and Hughes JP. (1978) *Chemical Hazards of the Workplace*. J.B. Lippincott, Philadelphia.

Schardein JL. (2000) *Chemically Induced Birth Defects*, 3rd Ed. Marcel Dekker, New York.

Scientific American Medicine (SciMed). (2015) Decker, New York. Updated monthly. Available at https://www.deckerip.com/products/scientific-american-medicine/ (accessed March 16, 2016).

Shannon MW, Borron SW, and Burns MJ. (2007) *Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose*, 4th Ed. Saunders, Philadelphia.

Shepard TH and Lemire RJ. (2010) *Catalog of Teratogenic Agents*, 13th Ed. Johns Hopkins University Press, Baltimore, MD.

Turco S and Davis NM. (1973) Clinical significance of particular matter: a review of the literature. *Hosp. Pharm.*, 8:137–140.

Wexler P. (Ed.) (2014) *Encyclopedia of Toxicology*, 3rd Ed. Academic Press, San Diego, CA.

Wiley-Interscience. (Ed.) (2007) *Wiley Handbook of Current and Emerging Drug Therapies*. John Wiley & Sons, Inc., Hoboken, NJ.


such as the Fragrance Industry Manufacturers Association and the Chemical Manufacturers Association have extensive toxicology databases from their research programs that are readily available to toxicologists of member companies. Texts that deal with specific target organ toxicity—neurotoxicity, hepatotoxicity, or hematotoxicity—often contain detailed information on a wide range of chemical structures. Published information sources like the *Target of Organ Toxicity* series (Taylor & Francis, now partway through a third set of revisions) are examples of the types of publications that often contain important information on many industrial chemicals that may be useful either directly or by analogy. Upon discovery that the material one is evaluating may possess target organ toxicity, a cursory review of these types of texts is warranted.

In the last decade, for most toxicologists the online literature search has changed from an occasional, sporadic activity to a semicontinuous need. Usually, in many companies, nontoxicology-related search capabilities are already in place. Therefore, all that is needed is to expand the information source to include some of the databases that cover the types of toxicology information one desires. However, if no capabilities exist within an organization (increasingly the case), one can approach a university,

consultant, or a private contract laboratory and utilize their online system at a reasonable rate. It is of course possible to access almost all of these sources from home (or home office) using a personal computer. The major available online databases are as follows:

A. *National Library of Medicine*. The National Library of Medicine (NLM) information retrieval service contains the well-known and frequently used Medical Information Online (MEDLINE), Toxicology Information Online (TOXLINE), and CANCERLIT databases. Databases commonly used by toxicologists for acute data in the NLM service are the following:
   1. TOXLINE is a bibliographic database covering the pharmacological, biochemical, physiological, environmental, and toxicological effects of drugs and other chemicals. It contains approximately 1.7 million citations, most of which are complete with abstract, index terms, and CAS Registry Numbers. TOXLINE citations have publication dates of 1981 to the present. Older information is on TOXLINE 65 (pre-1965 through 1980).
   2. MEDLINE is a database containing approximately 7 million references to biomedical journal articles published since 1966. These articles, usually with an English abstract, are from over 3000 journals. Coverage of previous years (back to 1966) is provided by back files, searchable online, that total some 3.5 million references.
   3. Toxicology Data Network (TOXNET) is a computerized network of toxicologically oriented data banks. TOXNET offers a sophisticated search and retrieval package that accesses the following three subfiles:
      a. Hazardous Substances Data Bank (HSDB) is a scientifically reviewed and edited data bank containing toxicological information enhanced with additional data related to the environment, emergency situations, and regulatory issues. Data are derived from a variety of sources including government documents and special reports. This database contains records for over 4100 chemical substances.
      b. Toxicology Data Bank (TDB) is a peer-reviewed data bank focusing on toxicological and pharmacological data, environmental and occupational information, manufacturing and use data, and chemical and physical properties. References have been extracted from a selected list of standard source documents.
      c. Chemical Carcinogenesis Research Information System (CCRIS) is a National Cancer Institute-sponsored database derived from both short- and long-term bioassays on 2379 chemical substances. Studies cover carcinogenicity, mutagenicity, promotion, and cocarcinogenicity.
   4. Registry of Toxic Effects of Chemical Substances (RTECS) is the NLM's online version of the National Institute for Occupational Safety and Health's (NIOSH) annual compilation of substances with toxic activity. The original collection of data was derived from the 1971 Toxic Substances Lists. RTECS data contains threshold limit values, aquatic toxicity ratings, air standards, National Toxicology Program carcinogenesis bioassay information, and toxicological/carcinogenic review information. The NIOSH is responsible for the file content in RTECS and for providing quarterly updates to NLM: RTECS currently covers toxicity data on more than 106 000 substances.

E. *The Merck Index*. *The Merck Index* is now available online for up-to-the-minute access to new chemical entities.

### 3.1.5 Search Procedure

As mentioned in Section 3.1, chemical composition and identification information should already have been obtained before the chemical is to be searched. With most information retrieval systems, this is a relatively straightforward procedure. Citations on a given subject may be retrieved by entering the desired free-text terms as they appear in titles, keywords, and abstracts of articles. The search is then initiated by entering the chemical CAS number and/or synonyms. If you are only interested in a specific target organ effect—for instance, carcinogenicity—or specific publication years, searches can be limited to a finite number of abstracts before requesting the printout.

Often it is unnecessary to request a full printout (author, title, abstract). You may choose to review just the author and title listing before selecting out the abstracts of interest. In the long run, this approach may save you computer time, especially if the number of citations being searched is large.

Once you have reviewed the abstracts, the last step is to request photocopies of the articles of interest. Extreme caution should be used in making any final health hazard determination based solely on an abstract or nonprimary literature source.

### 3.1.6 Monitoring Published Literature and Other Research in Progress

Although there are a few other publications offering similar services, the *Life Sciences* edition of *Current Contents* is the publication most widely used by toxicologists for monitoring the published literature. *Current Contents* monitors