Third Edition

Regulatory Toxicology

Edited by **Shayne C. Gad**

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Preface

Regulatory requirements for the toxicologic safety testing assessment of products have become much more globally harmonized and scientifically complex since the second edition of this volume was published in 2001.

While there is clinical (human) testing for safety in some product areas (drugs, medical devices, and cosmetics), testing in animal models is still predominate. However, nonanimals or *in vitro* models time continues to gain importance for reasons of concern about animal welfare, economics, the need for greater sensitivity, and a better understanding of the mechanisms and causes of toxicity.

As the contents of this volume demonstrate, there now exists a broad range of *in vitro* models for use in either identifying or understanding most forms of toxicity. The availability of *in vitro* models spans both the full range of endpoints (irritation, sensitization, lethality, mutagenicity, and developmental toxicity) and the full spectrum of target organ systems (skin, eye, heart, liver, kidney, nervous system, etc.). This volume devotes chapters to each of these specialty areas from a perspective of presenting the principal models and their uses and limitations.

Chapters that overview the principles involved in the general selection and use of models and that address the issues of safety concerns and regulatory acceptance of these methods are also included.

While this volume seeks to achieve an overview of current practices and requirements (particularly in the non-medical areas), as in any such volume, portions will be dated but not obsolete. The authors and I hope this will provide a sound basis for broad understanding and utilization of these models and their continuing improvement.

Shayne C. Gad

Editor

Shayne C. Gad, BS (Whittier College, Chemistry and Biology, 1971) and PhD in Pharmacology/Toxicology (Texas, 1977), DABT, is the principal of Gad Consulting Services, a twenty-five-year-old consulting firm with nine employees and more than 500 clients (including 140 pharmaceutical companies in the US and 50 overseas). Prior to this, he served in director-level and above positions at Searle, Synergen, and Beckton Dickinson. He has published 50 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 40 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 (Society of Toxicology) specialty sections. He has direct involvement in the preparation of Investigational New Drug applications (INDs, 115 successfully to date), New Drug Application (NDA), Product License Application (PLA), Abbreviated New Drug Application (ANDA), 501(k), Investigational Device Exemption (IDE), Common Technical Document (CTD), clinical data bases for phase 1 and 2 studies, and Premarket Approval Applications (PMAs). He has consulted for the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), and National Institutes of Health (NIH), has trained reviewers, and has been an expert witness for the FDA. He has also conducted the triennial toxicology salary survey as a service to the profession for the last 29 years.

Dr. Gad is also a retired Navy officer with more than 26 years in service.

Contributors

Sol Bobst
Nexeo Solutions
Woodlands, Texas

John A. Budny
PharmaCal Ltd
Westlake Village, California

Denese A. Deeds
Co-Founder, Senior Consultant
Industrial Health & Safety Consultants, Inc.
8 Huntington Street, Suite 290
Shelton, Connecticut 06484 USA

George DeGeorge
MB Research Labs
Spinnerstown, Pennsylvania

Shayne C. Gad
Gad Consulting Services
Raleigh, North Carolina

Elliot Gordon
Elliot Gordon Consulting LLC
Princeton Junction, New Jersey

Robin C. Guy
Robin Guy Consulting LLC
Lake Forest, Illinois

A. Wallace Hayes
Department of Environmental Health
Harvard School of Public Health
Andover, Massachusetts

Robert W. Kapp
BioTox
Monroe Township, New Jersey

M. Yusuf Khan
Technical Specialist
Cummins Inc.
Columbus, Indiana

Richard C. Kraska
Chief Scientific Officer
GRAS Associates LLC
Fort Myers, Florida

Chada S. Reddy
Associate Professor
Biomedical Sciences
University of Missouri

Elizabeth Roberts
Global Head of Safety
Dechra Veterinary Products, LLC
Raleigh/Durham, North Carolina

Edward V. Sargent
EV Sargent LLC
Clearwater, Florida

Clint Skinner
Skinner Associates
Creston, California

Charles B. Spainhour
Calvert Laboratories, Inc
Scott Township, Pennsylvania

Dexter W. Sullivan, Jr.
Gad Consulting Services
Raleigh, North Carolina

Alicia A. Taylor
Environmental Toxicologist/Senior Scientist
Exponent ExoSciences Practice
Seattle, Washington

Bennett Varsho
MB Research Labs
Spinnerstown, Pennsylvania

1 Introduction

Shayne C. Gad

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HISTORICAL PERSPECTIVE

Safety and toxicity testing (also called safety assessment or biocompatibility testing in different regulatory venues) is a necessary and vital part of bringing any chemical- or biological-containing and technologically advanced product to market under acceptable conditions of safe use. Stripped of its technical essence, toxicological testing could be described as the process of giving large amounts of commercial products to either large numbers of experimental animals or *in vitro* test systems, which are then exhaustively studied either as a whole or their component materials and measured for evidence of adverse effects. This, of course, oversimplifies the process and understates the purpose of such testing, which brings us to the question, what exactly is the purpose of such testing? Simply put, a great deal of toxicological testing and research is performed to comply with governmental regulations. While there are moral and ethical reasons for testing products prior to human exposure, testing requirements are codified by the law on a global scale. Ours, after all, is a civilized society. Many books and texts on the science of toxicology have been published in the 15 years since the previous edition of this book. It remains an expanding field with conflicting attempts to harmonize regulations globally, while creating precisely defined requirements in the face of an ever evolving technology field. The first edition of *Casarett and Doull's Toxicology* had only 482 pages in 1975, while the eighth edition in 2013 had 1,454 large format pages.

Other primary texts on the science of toxicology are listed in Table 1.1. In most of these texts, the emphasis is, rightfully, on the science and technology of toxicology. Most include a chapter on regulatory toxicology, yet most students receive at best a perfunctory introduction to regulatory concerns—usually an overview of Good Laboratory Practices (GLPs). For most doctoral students in toxicology, the GLPs are only a distant drone that hampers and confuses real science with meaningless procedures and paperwork. As a result, most contract lab or regulatory toxicologists begin their careers with little basic cognizance of the regulations that will govern the context, if not the content, of the job or product and this is just the beginning of what is to come. As this book seeks to make clear, virtually all commercial products have to meet regulatory toxicology requirements in their approval for market entry, manufacturing, distribution, and disposal. It is the object of this book to address this regulatory gap. This is a scientist's, engineer's, and manager's guide to these globally spanning regulations. We presume that the reader has a toxicological background and is familiar with basic study designs and terminology. The coverage here is neither exhaustive nor

TABLE 1.1
Key Safety Assessment Reference Texts

Text	Edition	Author, Year
Burger's Medicinal Chemistry and Drug Discovery	7th	Abraham (2010)
Documentation of the Threshold Limit Values and Biological Exposure Indices	7th	ACGIH (2012)
Handbook of Pharmaceutical Additives	3rd	Ash and Ash (2007)
Handbook of Food Additives	3rd	Ash and Ash (2008)
General and Applied Toxicology	3rd	Ballantyne et al. (2009)
Patty's Toxicology	6th	Bingham and Cohrssen (2012)
Martindale: The Complete Drug Reference		Brayfield (2014)
Registry of Toxic Effects of Chemical Substances (RTECS)		CDC (2018)
Contact Dermatitis		Cronin (1980)
Medical Toxicology	3rd	Dart (2004)
Toxicology of Drugs and Chemicals		Deichmann and Gerard (1996)
Pharmacotherapy: A Pathophysiologic Approach	9th	Dipiro et al. (2014)
Inactive Ingredient Database		FDA (2018)
Clinical Toxicology		Ford (2001)
Acute Toxicology Testing	2nd	Gad and Chengelis (1998)
Clinical Toxicology of Commercial Products	5th	Gosselin et al. (1984)
Toxicology of the Eye	4th	Grant (1993)
Hamilton and Hardy's Industrial Toxicology	6th	Harbison et al. (2015)
Haye's Principles and Methods of Toxicology	6th	Hayes an Kruger (2014)
Casarett and Doull's Toxicology: The Basic Science of Poisons	8th	Klaassen (2013)
Carcinogenically Active Chemicals: A Reference Guide		Lewis (1991)
Sax's Dangerous Properties of Industrial Materials	12th	Lewis (2012)
Annual Report on Carcinogens	14th	NTP (2016)
The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals	15th	O'Neil (2013)
Physician's Desk Reference	71st	PDR (2017)
Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens	6th	Pohanish (2011)
Chemical Hazards of the Workplace		Proctor and Hughes (1978)
Chemically Induced Birth Defects	3rd	Schardein (2000)
Scientific American Medicine	Monthly	Decker (2018)
Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose	4th	Shannon et al. (2007)
Catalog of Teratogenic Agents	13th	Shepard and Lemire (2010)
Clinical Significance of Particular Matter: A Review of the Literature		Turco and Davis (1973)
Encyclopedia of Toxicology	3rd	Wexler (2014)
Wiley Handbook of Current and Emerging Drug Therapies		Wiley-Interscience (2007)

encyclopaedic, but provides a guide to current global regulations for a toxicologist, health scientist, or other professional who has little legal interest or training. The central focus of this book is on the use of toxicology in a regulatory and legal arena. The science of toxicology is a secondary concern and, in fact, is discussed in only a cursory fashion.

Other than as an instrument of torture, war, and execution, the use of toxicology by government is a relatively new phenomenon. While the appropriate use of chemicals has been a central part of the industrial (technological and biotechnological) revolution that has resulted in a high standard of living, the unrestricted sale, use, and disposal of chemicals has resulted in more than a few problems. For a variety of factors involved in modern technology (as with centralization of the food supply) and urbanization in the nineteenth century, large numbers of people have increasingly come

into contact with toxic materials and have limited understanding of the consequences and no control over such exposures. Episodes of mass poisoning have often resulted, now increasingly associated with terrorism. Such incidents in the US have bolstered the growth of various consumer activist and environmental protectionist organizations (some of which, despite noble intentions, verge on luddism and hysterical technology phobia).

It was perhaps inevitable that those in government would find it politically wise to enact laws to regulate the preparation and distribution of food products, drugs, medical devices, consumer products, and chemicals in commerce. For example, in 1901, a diphtheria epidemic broke out in St. Louis. It was eventually linked to improperly manufactured diphtheria toxin. In response to the public outcry, the United States Congress passed the Virus Act of 1902. Among other things, this dictated that only licensed establishments could introduce vaccines, serums, or antitoxins into interstate commerce. Thus, the modern era of government regulations in the United States was born. The process has followed similar paths globally, although with different timelines.

REGULATIONS AND AGENCIES

Toxicological data are required to meet a vast array of legal and regulatory purposes, particularly in the areas of product development, registration, and regulation. In addition, not only are toxicological data required, but often the specific procedures for generating and recording data (e.g., GLPs) are also dictated by regulations.

Bureaucracies exist that regulate the production, testing, and distribution of just about all commercial products. The global regulations and regulatory bodies are the focus of this book, though an emphasis on the United States, the European Union, and Japan remains. The primary US regulations and responsible agencies are summarized in Table 1.2. In the US, the two main regulatory bodies covering most chemicals in commerce of any nature are the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA).

The roles of the FDA in the regulation of human pharmaceuticals, biologics, and medical devices, veterinary drugs, food additives, and cosmetics (to the extent that they are regulated) are discussed in Chapters 2 through 7, respectively. Consumer products are covered in Chapter 8. The role of the EPA in regulating pesticides (as defined by the Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA) and industrial non-pesticide chemicals (as defined by the Toxic Substances Control Act, or TSCA) is covered in Chapters 9 and 10. Manufacturing and distribution of industrial chemicals is found in Chapter 11.

The Consumer Product Safety Commission (CPSC) is responsible for chemicals containing products not covered by the FDA or EPA. This includes items such as soaps, household cleansers, fire extinguishments and retardants, and paint and artist's supplies. The CPSC is primarily covered in Chapter 8. Toxicological information is required by manufacturing employers in order to comply with occupational health and safety regulations covered in Chapter 11. Scientists interested in laboratory management must realize that worker safety is not simply a manufacturing concern. The Occupational Safety and Health Administration (OSHA) has recently promulgated safe laboratory working standards that dictate certain laboratory work practices. Ensuring clean water and air is covered in Chapter 12. Special cases such as California Proposition 65, increasingly complex safety data sheets for use in communicating potential hazards of products in transport, GMO (genetically manufactured organism) in the food chain, tobacco and marijuana, and oversight regulations are addressed in Chapters 13–16.

Each chapter has been authored by a toxicologist with experience in the specific product type. While style and substance may vary, each author focuses on the following:

- History that led to original legislation: What were the major social and historical events that led to the development of the original legislation and major subsequent changes?
- Administrative divisions and responsibilities for each agency.

TABLE 1.2
Summary of US Federal Regulations

Category	Agency	Act	Acronym	Law	Regulations
General chemical	EPA	Toxic Substances Control Act, 1976	TSCA	15 USC 2601	40 CFR 700-700
Pesticides	EPA	Federal Insecticide, Fungicide, and Rodenticide Act, 1972	FIFRA	7 USC 136	40 CFR 162-180
Human pharmaceuticals	FDA	Federal Food, Drug, and Cosmetic Act, 1938; numerous amendments		21 USC 301	21 CFR 200-499 600-680
Human medical devices	FDA	Federal Food, Drug, and Cosmetic Act, 1938; amendment in 1976		21 USC 307	21 CFR 800-895
Veterinary medicines	FDA	Federal Food, Drug, and Cosmetic Act, 1938; numerous amendments		21 USC 301	21 CFR 500-589
Food additives	FDA	Federal Food, Drug, and Cosmetic Act, 1938; numerous amendments		21 USC 301	21 CFR 170-189
Human over-the-counter and cosmetics	FDA	Federal Food, Drug, and Cosmetic Act, 1938; numerous amendments		21 USC 301	21 CFR 300-391 700-790
Consumer products	CPSC	Federal Hazardous Substances Act, 1960; numerous amendments	FHSA	15 USC 1261	16 CFR 1500-1512
	CPSC	Consumer Product Safety Act, 1972; numerous amendments		15 USC 2051	16 CFR 1000-1406
Worker safety	OSHA	Occupational Safety and Health Act, 1970	OSHA	29 USC 651	29 CFR 1910-1926
Animal care and use	USDA	Animal Welfare Act, 1966; amended 1970, 1976, and 1985			9 CFR 3

- Descriptions and discussion of the basic documents each agency/division requires to be filed.
- The toxicity data needs.
- The use of these data in some form of risk analysis.

While the emphasis of this book is on the regulations involved in causing testing to occur for product safety and environmental and manufacturing practices, there are other regulations that govern the manner in which this information is generated or gathered. These are the GLP regulations and the animal welfare laws, which are covered in Chapter 16.

NON-GOVERNMENTAL ORGANIZATIONS

A significant part of the regulatory process is actually not performed by government agencies, but rather by non-governmental organizations (NGOs). Most NGOs have an historical basis or origin in practice from years past and tend to have been created by professional societies, regulated industries, or both in coordination with government.

NGOs tend to regulate by developing standards for various things or operations. Examples are animal care American Association Laboratory for Animal Science (AALAS), marker exposure standards for chemicals, test methods for assessing toxicity or suitability of non-health care products American Society for Testing and Materials (ASTM), determinations of relative hazard of human carcinogenicity International Agency for Research on Cancer (IARC), harmonizing international

standards for assessing safety of drugs and biologics International Conference on Harmonization (ICH), international standards for devices and for quality assurance (ISO), and specifications for drug potency and biocompatibility (USP, EU, BP, Japanese, and other pharmacopoeias). The standards established are incorporated officially or unofficially into government-enforced legal requirements.

INTERNATIONAL HARMONIZATION

With the development of a true global economy and the moves toward removing trade barriers and free market worldwide, there has been significant progress toward standardizing regulatory requirements for establishing the safety of both drugs and medical devices. Throughout this volume, the chapters present not just requirements in the US, but also point out the differences (and agencies) associated with key other countries.

The process of resolving differences in regulatory requirements between countries is called harmonization and it has been led by two NGOs—the International Conference on Harmonization (ICH) for drugs and International Organization for Standardization (ISO) for medical devices. The three largest markets are the European Union (which encompasses most of Western Europe), Japan, and the US. The latter two are governed by single national governments, while the EU has a double layer of the Union's government (headquartered in Brussels) and separate national governments. The process of achieving harmonized standards has taken years, going through a series of steps. But it is now almost complete.

REGULATIONS ON THE WEB

Another change of striking proportions is that one no longer needs to wait for (and order) paper copies of regulations and guidelines. These are widely available online from the appropriate websites. For example, one can go to www.fda.gov/cder for the text of recent or new regulations and guidelines. In some cases, such as with the ISO, they must be purchased. A summary of available websites is presented in Appendix 2.

GOOD LABORATORY PRACTICES

The GLPs were first issued by the FDA in 1978 in response to a variety of instances that led the agency to conclude that some of the data it had obtained were not trustworthy. As of September 2016, a major update of GLPs has been proposed. FDA GLP regulations (21 CFR part 58, revised as of April 1, 2017) are routinely reviewed and updated and are available in their most current form through the e-CFR database (www.ecfr.gov). The EPA has two sets of GLPs: one for the Office of Pesticides (FIFRA) and one for the Office of Toxic Substances (TSCA). They are similar to each other and to the FDA's regulations. The inclusion of the FDA GLPs should be sufficient to give the reader a taste of the regulations. The GLPs require that all pivotal preclinical safety studies (those used to make direct decisions on human exposure) be conducted under a well-defined protocol according to written standard operating procedures by (documented) trained personnel under the direction of a study director. All work must be reviewed by an independent Quality Assurance Unit (QAU).

Record-keeping requirements are rigorous. For example, no notebook entry can be changed without a footnoted explanation, and the change must be made in such a way that the original entry is still legible.

Both the EPA and the FDA have offices of compliance. There are field auditors who inspect toxicity research facilities. All laboratories that conduct toxicological assessments that are submitted to either the EPA or the FDA must undergo periodic capability audits (approximately every 2 years). One should be prepared for a team of auditors to show up without advance warning and to review facilities and procedures in excruciatingly minute detail. At the end of an FDA inspection, the

auditors will issue an Enforcement Inspection Report (EIR) to the agency and a report on inspections (Form 483) to the facility. This will be reviewed with facility management in a wrap-up meeting. After receiving an official EIR, the facility has 90 days to respond in writing to the agency. If the agency finds the answers satisfactory, the case file will be closed. The inspectors will issue requests to the facility on what may be required to address any deficiencies. These may be either *voluntary only* action or *mandatory action required* requests. Failure to comply with the GLPs or with mandatory action requests can result in a facility being disqualified. That is, its work will no longer be accepted by the agency. If the inspectors find reasonable grounds and suspect illicit activity (data falsification), the findings can be turned over to the Justice Department for possible criminal activity. Records can be sealed and impounded.

ANIMAL USE AND WELFARE

Toxicology flowered in the twentieth and twenty-first centuries, largely as a result of rapidly expanding chemical technologies and the resulting social and legal pressures, but also as a result of increased scientific sophistication. The use of intact, live animals in toxicological research has been, and shall remain, a vital and necessary part of this progress. The practice of using animals has come under organized and vituperative attack by animal rights activists. This has culminated in the passage by Congress of the Animal Welfare Act in 1990 and the subsequent development by the Department of Agriculture of the Animal Welfare regulations. Current influences across the entire realm of toxicology (safety assessment) include public concern with the use of animals in research and testing and the overstatement of cases of cruelty to animals and of the current status of alternative or *in vitro* models. This has, however, stimulated extensive reductions and refinements in animal use and replacement with *in vitro* and computer modeling alternatives in an increasing number of cases.

However, total replacement of animals is not possible in the foreseeable future. While such replacement is readily possible for some uses, these are either when no regulatory submission of test results is required (in the US) or for some uses in meeting international regulatory requirements.

The key assumptions underlying modern toxicology are as follows:

1. Other organisms can serve as accurate predictive models of toxicity in humans.
2. Selection of an appropriate model is essential to accurate prediction in humans.
3. Understanding the strengths and weaknesses of any particular model is essential to understanding the relevance of specific findings to humans.

The nature of models and their selection in toxicologic research and testing have only recently become the subject of critical scientific review. Usually in toxicology, when we refer to *models*, we actually mean *test organisms*. But, in fact, the ways in which parameters are measured (and in which parameters are measured to characterize endpoint of interest) are also critical parts of the model (or, indeed, may actually constitute the *model*).

Although there have been accepted principles for test organism selection, these have not generally been the final basis for such selection. It is a fundamental hypothesis of both historical and modern toxicology that adverse effects caused by chemical entities in higher animals are generally the same as those induced by those entities in humans (Gad, 2015). There are many who point to individual exceptions to this and conclude that the general principle is false. Yet, as our understanding of molecular biology advances and we learn more about the similarities of structure and function of higher organisms at the molecular level, it becomes clear that the mechanisms of chemical toxicity are largely identical in humans and animals. This increased understanding has caused some of the same people who question the general principle of predictive value to, in turn, suggest that our state

of knowledge is such that mathematical models or simple cell culture systems could be used just as well as intact animals to predict toxicities in humans. This last suggestion also misses the point that the final expressions of toxicity in humans or animals are frequently the summation of extensive and complex interactions at cellular and biochemical levels. Zbinden has published extensively in this area, including a very advanced defense of the value of animal models. Lijinsky has reviewed the specific issues about the predictive value and importance of animals in carcinogenicity testing and research. Although it was once widely believed (and still is believed by many animal rights activists) that *in vitro* mutagenicity tests would entirely replace animal bioassays for carcinogenicity, this is clearly not the case on either scientific or regulatory grounds. Although there are differences in the responses of various species, including humans, to carcinogens, the overall predictive value of such results, when tempered by judgement, is clear. At the same time, well-reasoned use of *in vitro* or other alternative test model systems is essential to the development of a product safety assessment program that is both effective and efficient.

LAW VERSUS REGULATION

The law is embodied in the documents written, debated, and passed by Congress and then approved by the President. It is then incorporated into the US Code of Federal Regulations. Part of the code includes the federal agency responsible for administering the law. The responsible agency will then devise and propose regulations that it believes will meet the intent of Congress. Regulations are the enforcing rules of the law and thus have an impact on the activities of toxicologists working in industrial settings. Both proposed (for comment) and final rules and regulations are published in the Federal Register. When final rules are published, they include a response by the agency on the comments received concerning proposed regulations.

Regulations are organized in the Code of Federal Regulations using the following system:

TITLE
- CHAPTER (denoted by Roman numeral, uppercase)
  - PART (denoted by Arabic numeral)
    - SUBPART (denoted by letter, uppercase)
      - SECTION (decimal point, followed by Arabic numeral)
        - SUBSECTION (denoted by uppercase Roman numeral)
          - PARAGRAPH (denoted by lowercase letter in parentheses)

Further subdivisions are denoted by parentheses, Arabic numerals, and Roman numerals.

For example, Title 20, Chapter I of the Code of Federal Regulations covers all FDA Regulations. Subchapter F covers biologics. Subpart B covers establishment standards and Section 600.10 specifically covers personnel. Paragraph (c) covers restrictions on personnel, and part two of the paragraph covers the wearing of protective clothing.

Since parts and sections are enumerated without redundancy (there is no Part 600 in any other chapter of Title 20), it is customary not to specify subtitle, chapter, subchapter, or subpart in making references to the Code of Federal Regulations. Thus, the reference just described would be denoted 21 CFR 600.10 (c)(2).

Regulations are not forever. They are continually being added to, deleted, and modified. There is an entire industry based on keeping industry and the public aware of such changes, their proposals, and impacts by means of an array of newsletters. Some of the more prominent of these are summarized in Table 1.3.

A huge number of acronyms are now commonly used in both toxicology and regulatory actions. Appendix 1 presents an extensive listing of these. A great deal of information is now available on the Internet. Appendix 2 presents the URLs of key regulatory and government sites.

TABLE 1.3
Regulatory Newsletters

Newsletter	Publisher	Coverage
Federal Register	US Government	All proposed and final rules and guidelines
FDA Medical Bulletin	FDA	New indications, changes in claims, toxicity warnings
Pesticide & Toxic Chemical News	Food Chemical News, Inc.	FIFRA, TSCA issues, regulatory actions, guideline changes
BELLE Newsletter	University of Massachusetts Public Health	Biological effects of low-level exposure of chemicals in the environment
Animal Pharmaceuticals	PJB Publications	Animal health and nutrition
Washington Drug Letter	Washington Business Information, Inc.	Policy, problems, and so on, at the FDA
Warning Letter	Washington Information Source	FDA enforcement activities, inspections, and compliance
Covance Regulatory Review	Covance	Changes in FIFRA, TSCA, FDA regulations and operations, trials, and scientific news
F-D-C Reports (*pink sheets*) applicable to the pharmaceutical industry	F-D-C Reports, Inc.	Regulatory actions, scientific news, and business information
BioWorld Week	BioWorld publishing	Regulatory, scientific, and financial happenings in the biotechnology world

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2 Human Pharmaceutical Product Safety

Shayne C. Gad

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INTRODUCTION

The safety of therapeutic medicines (small and large molecules) is a global toxicology issue of the most obvious and longest-standing concern to the public. 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 understanding or knowing this risk in advance. 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 that establish how the safety of human pharmaceutical products are evaluated and established in the United States and the other major international markets. Two major changes since the last edition of this book are that (1) the process of international harmonization of safety assessment has produced nearly globally accepted guidelines for nonclinical safety testing, and (2) generic drugs have assumed a position comprising half of global sales, with the equivalent products for biologic drugs (*biosimilars*) starting to follow the same pattern (Greene, 2014). As a starting place, the history of these regulations will be reviewed, and the organizational structure of the Food and Drug Administration (FDA) will be briefly reviewed, along with the other quasi-governmental 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 that defines some key terms.

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.

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 Institute of Health) and Treasury Department.
1906	Passage of the 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 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 from Agriculture (now the Department of Health and Human Services) to the Department of Health, Education, and Welfare (HEW).
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 Drugs 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 that for devices, safety as well as effectiveness be proven.
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 United States Drug Export Amendment Act of 1986. Permitted the export of drugs outside the US 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).
1994	Orphan Drug Amendment.

(*Continued*)

TABLE 2.1 (*Continued*)
Important Dates in US Federal Drug Law

Year	Event
1997	The Food and Drug Administration Modernization Act, to streamline the drug and device review and approval process.
2002, 2007, 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.

1906: Pure Food and Drug Act

As so eloquently discussed by Temin in *Taking Your Medicine: Drug Regulation in the United States* (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 ten 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, there was little mention of toxicity testing. When Harvey Wiley, chief of the Bureau of Chemistry, Department of Agriculture and a 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 on animals (Anderson, 1958). Ironically, work that led to the establishment of the FDA 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 post-marketing criminal charges. Efficacy was not a consideration until 1911, when the Sherley Amendment outlawed fraudulent therapeutic claims.

1938: Food, Drug, and Cosmetic Act

The present regulations are largely shaped by the law passed in 1938. This will, therefore, be discussed in some detail. The story of the 1938 Food, Drug, and Cosmetic Act (FDCA) actually started 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 it in the 2010s were not practiced. Most medicines were, in fact, self-prescribed. Only a relatively small number of drugs were sold via physician's 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 one 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 that 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. Pre-marketing 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 rime, 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 (tradition has it that if it had not been for the First Lady, Eleanor Roosevelt, 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 the efforts of the various lobbying groups, there was no popular interest or support for the bill. At 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, committee meetings and hearings, lobbying, and House/Senate conferences. The details of this parliamentary infighting make for fascinating history, but they are outside the scope of this book. For an excellent history of the period, see *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 that was contrary to general medical practice and opinion. The definition of a drug was broadened to include devices used for medical purposes.* *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—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 the sensationalized Chamber of Horrors exhibition, in which the toxicity of a variety of useless medicines was clearly displayed), mimeographed circulars, speaking engagements, posters, and so on.

* 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.

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 Massengil Company was not one of the industry giants, but neither was it a *snake oil peddler*. The company's chief chemist, Harold Wackins, 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. 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 the six deaths in his area that were attributable to the elixir. At the time, no product of Massengil stood accepted by the Council on Pharmacy and Chemistry, and the Council recognized no solution of sulfanilamide. The AMA telegraphed Massengil, requesting samples of the preparation for testing. Massengil 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 health risks and launched an investigation through its Kansas City station. By October 20, when at least 14 people had died, Massengil 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. Massengil 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 was fined a total of $26,000 (the largest fine ever levied under the 1906 law).

The Massengil 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 Pharmacopoeia (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 in to 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. It 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 issue of which agency was to control advertising of drugs was still festering 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 in 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 it 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 that 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 D. 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 the bill into law.

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, while 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. 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) 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 groundswell 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, also with little support.

As in 1938, a tragic incident would intercede in the legislative process—1961 saw the development of the thalidomide tragedy. An antianxiety agent marketed in Europe, thalidomide was prescribed for pregnancy-related nausea (*morning sickness*) and depression. It was 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. Merrill Company had applied for a New Drug Application (NDA) for thalidomide in the US 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 out 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 (IND). 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 amendment, 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 that 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 the Prescription Drug User Fee Act (PDUFA) and 1997 with the 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.

1992, 1997, 2002, 2007, and 2012: Prescription Drug User Fee Act and Food and Drug Administration Modernization Act

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 on the subject (Hutt, 1983a, 1983b). 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, 1983b)—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, 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 INDs was decreasing and the new drug application success rate was 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%).

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. While PDUFA was successful in decreasing review times, it 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, and manufacturing changes). 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, introduced by Senator

Paul Wellstone (D-MN) and Rep. Ron Weyden (D-OR), focused more on medical devices but still 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 observed, "a measure of the

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
	102.	Definitions
	103.	Authority to assess and use drug fees
	104.	Annual reports
	105.	Savings
	106.	Effective date
	107.	Termination of effectiveness
B. Other Improvements	111.	Pediatric studies of drugs
	112.	Expanding study and approval of fast track drugs
	113.	Information program on trials for serious disease
	114.	Healthcare economic information
	115.	Manufacturing changes for drugs
	116.	Streamlining clinical research for drugs
	118.	Data requirements for drugs and biologics
	119.	Content and review of applications
	120.	Scientific advisory panels
	121.	Positron emission tomography
	122.	Requirements for radiopharmaceuticals
	123.	Modernization of regulation
	124.	Pilot and small-scale manufacture
	125.	Insulin and antibiotics
	126.	Elimination of certain labeling requirements
	127.	Application of federal law to pharmacy compounding
	128.	Reauthorization of clinical pharmacology program
	129.	Regulation of sunscreen products
	130.	Report of post-marketing approval studies
	131.	Notification of discontinuance of a life-saving product
II. Improving Regulation of Devices	201.	Investigational device exemptions
	202.	Special review for certain devices
	203.	Expanding humanitarian use of devices
	204.	Device standards
	205.	Collaborative determinations of device data requirements
	206.	Premarket Notification
	207.	Evaluation of automatic Class III designation
	208.	Classification panels
	209.	Certainty of review timeframes
	210.	Accreditation of person for review of premarket notification reports
	211.	Device tracking
	212.	Post-market notification
	213.	Reports

(*Continued*)

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

Title/Subtitle	Section	
	214.	Practice of medicine
	215.	Non-invasive blood glucose meter
	216.	Data relating to premarket approval: product development protocol
	217.	Number of required clinical investigations for approval
III. Improving Regulation of Food	301.	Flexibility for regarding claims
	302.	Petitions for claims
	303.	Health claims for food products
	304.	Nutrient content claims
	305.	Referral statements
	306.	Disclosure of radiation
	307.	Irradiation petition
	308.	Glass and ceramic ware
	309.	Food contact substance
IV. General Provisions	401.	Dissemination of information new uses
	402.	Expanded access of investigational therapies and diagnostics
	403.	Approval of supplemental applications for approved products
	404.	Dispute resolution
	405.	Informal agency statements
	406.	FDA mission and annual report
	407.	Information system
	408.	Education and training
	409.	Centers for education and research on therapeutics
	410.	Mutual recognition of agreements and global harmonization
	411.	Environmental impact review
	412.	National uniformity for nonprescription drugs and cosmetics
	413.	FDA study of mercury in drugs and foods
	414.	Interagency collaboration
	415.	Contracts for expert review
	416.	Product classification
	417.	Registration of foreign establishments
	418.	Clarification of seizure authority
	419.	Interstate commerce
	420.	Safety report disclaimers
	421.	Labeling and advertising compliance with statutory requirements
	422.	Rule of construction
V. Effective Date	501.	Effective date

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" (Marwick, 1998). The FDA has identified these various tasks, regulations, and guidances necessary for the implementation of FDAMA. 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 US 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.

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 (the IND) and premarket approval (the NDA) of new drugs. Regulations pertaining to INDs 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 Laboratory 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 *National and International Drug Safety Guidelines* (Alder and Zbinden, 1988), but key points are presented in this chapter.

OVERVIEW OF US REGULATIONS

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″ × 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, and so on. 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.

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 (IND) 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 IND (covered in 21 CFR 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 is 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). Second, 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 (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.

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 (CMC) information
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

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, and so on. 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.

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 European Economic Community (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 (photohydrolysis) and toxicity (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).

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) that 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).

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 (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).

TABLE 2.4
Product Class Review Responsibilities

Center for Drug Evaluation and Review
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 Review
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

A current list of regulatory documents (including the most recent points to consider, or PTCs) can be found on the FDA website by accessing the FDA home page (www.fda.gov) and locating the *Regulatory Information*. The Regulatory Information site can also be accessed directly using the web address: http://www.fda.gov/RegulatoryInformation/default.htm.

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 2.5
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.

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 overseen primarily by the CDER (though some therapeutic or health-care 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 IND 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 (IND, IND[A]) are handled by the offices of Biological Products Review within the CBER.

For drugs, there is at least one non-governmental body that 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).

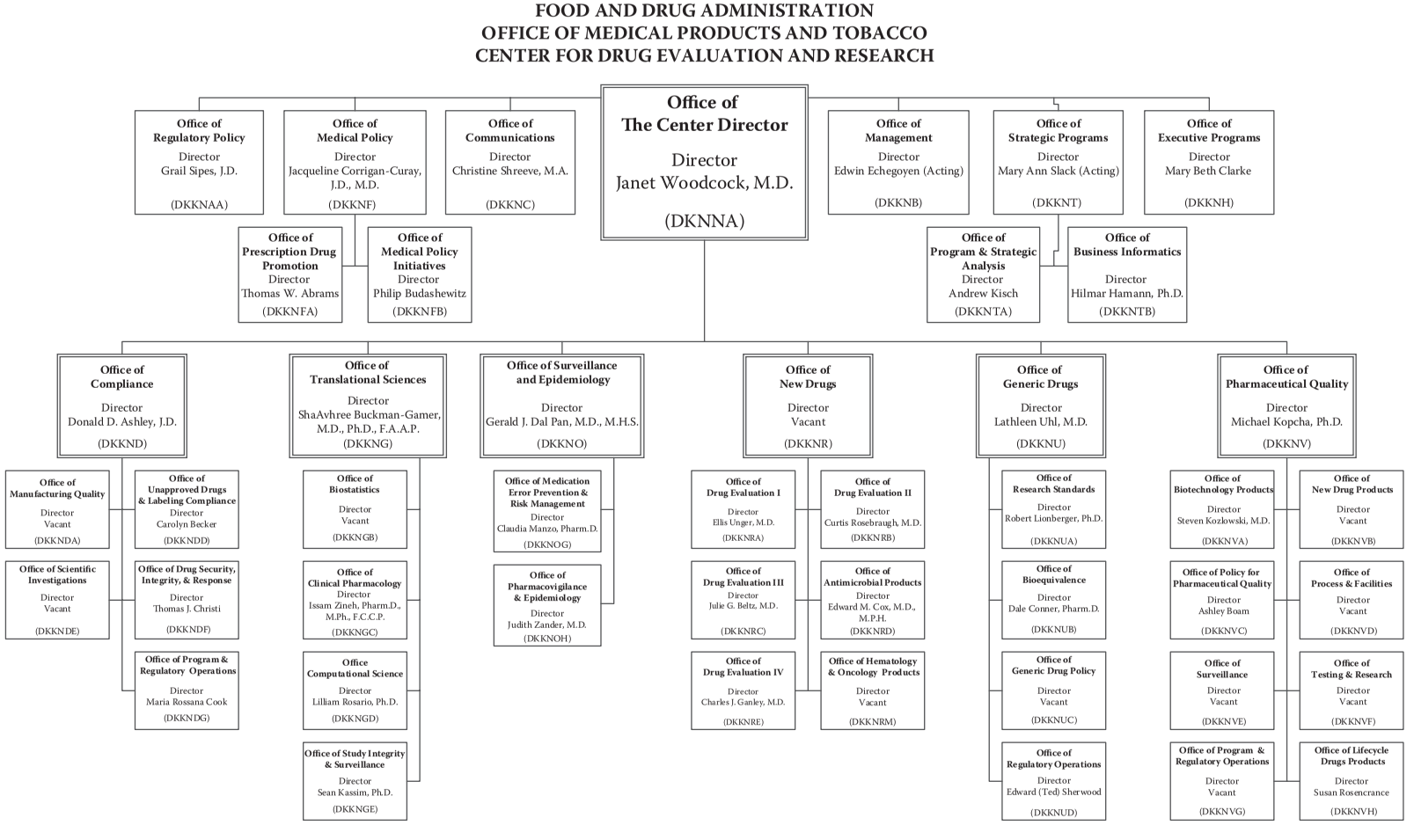

FIGURE 2.1 CDER. Accessed at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM439876.pdf.

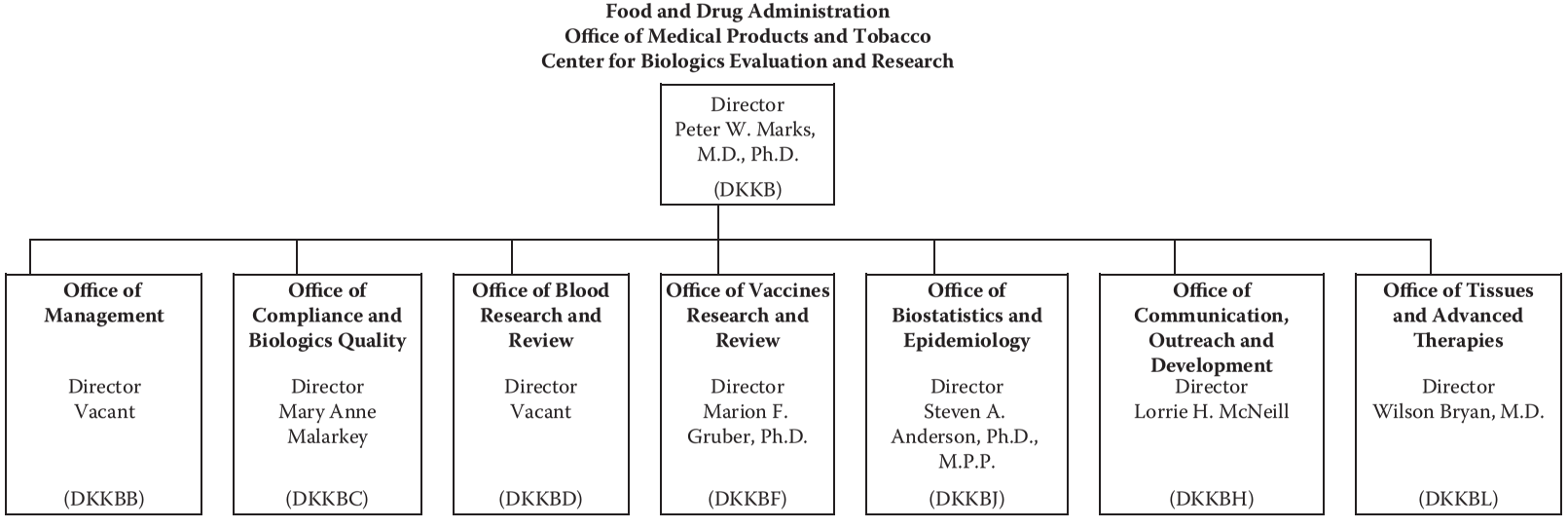

FIGURE 2.2 CBER. Accessed at: http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm347874.htm.

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 that 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 a 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.

TESTING GUIDELINES

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.

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. These are misleading in their apparent simplicity, however. 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.

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	2 Species; 2 weeks	For parentally administered drugs
	Up to 2 weeks	I	2 Species; 4 weeks	
		II	2 Species; up to 4 weeks	
		III, NDA	2 Species; up to 3 months	Compatibility with blood where applicable
	Up to 3 months	I, II	2 Species; 4 weeks	
		III	2 Species; 3 months	
		NDA	2 Species; up to 6 months	
	6 Months to unlimited	I, II	2 Species; 3 months	
		III	2 Species; 6 months or longer	
		NDA	2 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	4 Species; 5 days (3 hours/day)	
Dermal	Single application	I	1 Species; single 24-hour exposure followed by 2-week observation	Sensitization
	Single or short-term application	II	1 Species; 20-day repeated exposure (intact and abraded skin)	
	Short-term application	III	As earlier	
	Unlimited application	NDA	As earlier, but intact skin study extended up to 6 months	

(*Continued*)

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

Category	Duration of Human Administration	Clinical Phase	Subacute or Chronic Toxicity	Special Studies
Ophthalmic	Single application	I		Eye irritation tests with graded doses
	Multiple application	I, II, III	1 Species; 3 weeks, daily applications, as in clinical use	
		NDA	1 Species; duration commensurate with period of drug administration	
Vaginal or Rectal	Single application	I		Local and systematic toxicity after vaginal or rectal application in 2 species
	Multiple application	I, II, III, NDA	2 Species; duration and number of applications determined by proposed use	
Drug combinations		I, II, III, NDA	2 Species; up to 3 months	Lethality by appropriate route, compared to components run concurrently in 1 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 US 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.

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 toxicology) 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 a rabbit. Use of a rabbit was instituted as a result of the finding that thalidomide was a positive teratogen in a rabbit but not in a rat. On occasion, when a test article is not compatible with a rabbit, teratogenicity data in a 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 various 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.

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, and so on, 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 IND, 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 US, 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.
- *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.

Safety Pharmacology

Midway through 2001, the ICH and related regional regulatory authorities (such as the United States Food and Drug Administration [FDA], European Medicines Agency [EMA], and Japanese Ministry of Health, Labor and Welfare [MHLW]) implemented a new set of preclinical safety assessment requirements (to be completed before initiation of human clinical trials) 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. This is discussed in detail in Chapter 18 of Gad (2016), and in *Safety Pharmacology in Pharmaceutical Development: Approval and Post Marketing Surveillance* (Gad, 2012).

Local Tissue Tolerance

Not called out in ICH guidances but rather in the US and other pharmacopeia 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 for all routes except oral (Gad, 2016).

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 include:

- 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, and so on
- 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 to, for example, 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*—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 bio technology-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 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 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, due to their biological mechanism of action, may stimulate the proliferation of transformed cells. For instance, 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: rat, dog, or 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).

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 that 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 IND 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, the 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 routes 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 (1) the relationship of the dose to biological activity, (2) the relationship of the dose to toxicity, (3) the effect of route and/or schedule on activity or toxicity, and (4) 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 risks to the environment.

To date, cellular and gene therapy products submitted to the 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).

Cellular Therapies

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

Manipulation: Autologous, allogenic, or xenogenic cells that 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 that 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 that do not specifically fit the earlier. This group includes cellular therapies, such as extracorporeal liver assist devices.

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, as well as in vivo viral vectors, plasmid vectors, and vector producer cells.

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 that do not specifically fit under the earlier (e.g., tumor vaccines in which cells are cultured or transduced ex vivo with a vector).

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.

Preclinical Safety Evaluation

The goal of the preclinical safety evaluation includes recommendation of an initial safe starting dose and safe dose-escalation scheme in humans, identification of potential target organs of toxicity, identification of appropriate parameters for clinical monitoring, and identification of *at-risk* patient populations. 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 of traditional pharmaceuticals is that the focus is directed at asking specific questions across various product categories. Additionally, there is a consistent re-evaluation of the knowledge base to reassess real or theoretical safety concerns and hence re-evaluation of the need to answer the same questions across all product categories. In some cases, there may even be conditions that may not need specific toxicity studies—for example, when there is a strong efficacy model that is rationally designed to answer specific questions and/or there is previous human experience with a similar product with respect to dose and regimen.

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 (e.g., infections or pathologic sequelae and/or biological activity or receptor binding)
- Consideration of animal models of disease that may be better to assess the contribution of changes in physiologic or underlying physiology to safety and efficacy
- Determination of effect 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

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

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)

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.

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

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 2.6 and 2.7 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. With the development of more effective HIV therapies (protease inhibitors), cancer therapy is now 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 the 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 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, identifying those doses that produce either life-threatening or nonlife-threatening toxicity. Using the information from this first study, a second study in non-rodents (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 non-rodents 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 needs to be addressed. For genotoxicity, it is important to establish the ratio between cytotoxicity and mutagenicity. For 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 require additional studies. For example, a liposomal agent needs 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 is 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, and so on. The toxicity assessment studies on these more closely resemble those of more traditional pharmaceutical agents. Chronic toxicity, carcinogenicity, and full developmental toxicity (ICH A–B, C–D, E–F) assessments are required. For a more complete review, the reader is referred to DeGeorge et al. (1998).

Optical Isomers

The FDA (and similar 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) due to 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 basis (FDA, 1988; De Camp, 1989; Anonymous, 1992/2015; FDA, 2015) 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 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 (for instance, already on the market), then appropriate bridging guides need to be performed, comparing the toxicity of the isomer to that of the racemic mixture. The most common approach is to conduct a subchronic (3 months) and a segment II type teratology study with an appropriate *positive* control group that 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.

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 prescribing 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, "Pediatric Product Development" (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm) that lists such information. Interestingly, the focus has been on clinical trials and almost no attention has been given to the issue of appropriate preclinical toxicology studies that may be necessary to support such trials, while 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 authors considered opinion) in various animal models are given in Table 2.9. The table

TABLE 2.9
Comparison of Postnatal Development Stages

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

is somewhat inaccurate, however, due to differences 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 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 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 toxicity study of the new pharmaceutical agent in 3-day-old rats is not appropriate. Furthermore, if the proposed course of treatment in human 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), 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 also needs 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 must 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 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.

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 • 21 CFR part 601, subpart E • Section 506© 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 • 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 endpoint(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 endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint 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 endpoint)	• 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 • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A[b] OR • An application for a drug that has been designated as a qualified infectious disease product[a] OR • Any application or supplement for a drug submitted with a priority review voucher[c]

(*Continued*)

TABLE 2.10 (*Continued*)
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**
When to submit request	• With IND or after • Ideally, no later than the pre-BLA or pre-NDA meeting	• With IND or after • Ideally, no later than the end-of-phase 2 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 endpoint as a basis for approval and discussing the confirmatory trials, which should usually be already underway 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
Features	• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint 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)[d]
Additional considerations	• Designation may be rescinded if it no longer meets the qualifying criteria for fast track[e]	• Designation may be rescinded if it no longer meets the qualifying criteria for breakthrough therapy[f]	• Promotional materials • Confirmatory trials to verify and describe the anticipated effect on IMM or other clinical benefit • Subject to expedited withdrawal	• Designation will be assigned at the time of original BLA, NDA, or efficacy supplement filing

[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.

(*Continued*)

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

[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] 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.

[d] As part of its commitments in PDUFA V, 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.

[e] 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. of Appendix 1).

[f] 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. of Appendix 1).

Extracted from CDER and CBER (2014).

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 that 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 undergo the same FDA review process. A major difference, however, is the involvement of OOPD. A sponsor must request OOPD review. Once OOPD determines that a drug meets the criteria for orphan drug status, it will work with the sponsor to provide the assistance required under the Act. The OOPD does not review a product for approval. The IND/NDA process is still handled by the appropriate reviewing division for formal review. The Act does not waive the necessity for submission of an IND, nor 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.

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 to modern drug development in the middle part of the century, for reasons having to do with patentability, manufacturing costs, standardization, selectivity, and potency. 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 prescribed 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.

Types of New Drug Applications

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 EOC Directive 2001/83/EC, amended in July of 2008).

INTERNATIONAL PHARMACEUTICAL REGULATION AND REGISTRATION

International Conference on Harmonization

The ICH was established to make the drug regulatory process more efficient in the United States, Europe, and Japan. 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 non-tariff barriers to trade (Barton, 1998). The main purpose of the 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 the ICH, by the escalating cost of research and development. 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. Representation is summarized in Table 2.11. The biennial conference met regularly, 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

TABLE 2.11
ICH Representation

Country/Region	Regulatory	Industry
European Union	European Commission (2)	European Federation of Pharmaceutical Industries Associations (2)
Japan	Ministry of Health and Welfare (2)	Japanese 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 Area, Canadian Health Protection Branch	International Federation of Pharmaceutical Manufactures Associations (2), also provides the secretariat

() = number of representatives on the ICH steering Committee.

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 steps of review and revision, summarized in Table 2.12. So far, the ICH has proposed or adopted more than 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.

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]

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

[a] (ICH, 1997).

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	Clinical safety data management: Data elements for transmission of individual case safety reports	May 2005
E2C	Clinical safety data management: Periodic safety update reports for marketed drugs	May 1997
E2D	Definitions and standards for expedited reporting	November 2003
E2E	Pharmacovigilance planning	November 2004
E3	Structure and content of clinical study reports	November 1995
E4	Dose response information to support drug registration	March 1994
E5	Ethnic factors in the acceptability of foreign clinical data	February 1998
E6	Good Clinical Practice: Consolidated guideline; notice of availability	May 1996
E6A	GCP addendum on investigator's brochure	March 1995
E7	Studies in support of special populations: Geriatrics	June 1993
E8	Guidance on general considerations for clinical trials; notice	July 1997
E9	Draft 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
E12	Principles for clinical evaluation of new antihypertensive drugs	
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
M3	Guidance on nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals; notice	November 1997
Q1A	Stability testing of new drug substances and products	February 2003
Q1B	Stability testing of new drug substances and products	November 1996

(*Continued*)

TABLE 2.13 (*Continued*)
International Conference on Harmonization Guidelines

References	Guideline	Date
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
Q1F	Stability data package for registration applications in Climatic Zones III and IV	June 2006
Q2	Validation of analytical procedures: Text and methodology	October 1994
Q3A	Guideline on impurities in new drug substances	October 2006
Q3B	Guideline on impurities in new drug products	June 2006
Q3C	Guideline on impurities: Guideline for residual solvents	July 1997
Q4	Pharmacopeias	November 2007
Q4A	Pharmacopeias harmonization	November 2007
Q4B	Evaluation and recommendation of pharmacopoeial texts	November 2007
Q4B Annex 1	Evaluation and recommendation of pharmacopoeial texts: Residue on ignition/ sulphated ash general chapter	November 2007
Q4B Annex 2	Evaluation and recommendation of pharmacopoeial texts: Test for extractable volume of parenteral preparations general chapter	November 2007
Q4B Annex3	Evaluation and recommendation of pharmacopoeial texts: Test for particulate contamination: sub-visible particles general chapter	November 2007
Q5A	Quality of biotechnological products viral safety evaluation of biotechnology products derived from cell lines of human or animal origin	March 1997
Q5B	Quality of biotechnology products analysis of the expression construct in cells used for production of rDNA 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	Pharmaceutical development	November 2005
Q8 Annex	Pharmaceutical development annex	November 2007
Q9	Quality risk management	November 2005
Q10	Pharmaceutical quality system	May 2007
Q6A	Draft guidance on specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances; notice	November 1997
Q6B	Specifications: Test procedures and acceptance criteria for biotechnology products	February 1998

See Table 2.14 for current Safety Guidance list.

TABLE 2.14
ICH Current Guidelines Governing Nonclinical Safety Evaluation

Reference Number and Classification	Title	Adopted Originally	Revisions	Link to Document
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	Addendum on a Limit Dose dated July 17, 1997 and incorporated in November 2005; Revised on 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 & 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 & 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 Non Rodent Toxicity Testing)	September 2, 1998	N/A	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S4/Step4/S4_Guideline.pdf

(*Continued*)

TABLE 2.14 (*Continued*)
ICH Current Guidelines Governing Nonclinical Safety Evaluation

Reference Number and Classification	Title	Adopted Originally	Revisions	Link to Document
S5(R2) REPRODUCTIVE TOXICOLOGY	Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility	June 24, 1993	Addendum dated November 9, 2000 incorporated in November 2005	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S5_R2/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 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 PHARMACOLOGY STUDIES	The Non-Clinical 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 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 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 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

(*Continued*)

TABLE 2.14 (*Continued*)
ICH Current Guidelines Governing Nonclinical Safety Evaluation

Reference Number and Classification	Title	Adopted Originally	Revisions	Link to Document
S11 JUVENILE TOXICITY	Nonclinical Safety Testing in Support of Development of Pediatric Medicines	November 10, 2014 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 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 R2: June 11, 2009	http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf
M7R1 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 March 17, 2015.
All guidelines can also be accessed through the ICH website at http://www.ich.org/products/guidelines.html.

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 well as traditional GLP issues), and the "S" series having to do with safety. Guidelines can be obtained from the ICH secretariat, c/o of IFPMA, 30 rue de St.-Jean, PO Box 9, 1211 Geneva 18, Switzerland, or they can be downloaded directly from the ICH website (http://www.ich.org/products/guidelines.html). They are also published in the Federal Register. The guidelines of the "S" series have the most impact on toxicologists. The biggest changes having to do with toxicological assessment are summarized as follows.

Carcinogenicity Studies

Carcinogenicity studies are covered in Guidelines S1A, S1B, and S1C. The guidelines are almost more philosophical than technical. In comparison to the EPA guidelines, for example, the ICH guidelines contain little in the way of concrete study criteria (the number of animals or the necessity for clinical chemistry, for instance). 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.

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 a 6-month duration are recommended for the rodent, as rodents will also be examined in 2-year studies. For the nonrodent (dog, nonhuman primate, and pig), studies of a 9-month duration are recommended.

Developmental and Reproductive Toxicity

This was an area in which there was considerable international disagreement and the area in which the 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) has been standardized.
- New guidelines for fertility assessment studies (traditional segment I) with shortened 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.

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 B. Conception to implantation	Fertility and early embryonic development, including implantation	Males: 4 weeks premating, mating (1–3 weeks) plus 3 weeks postmating Females: 2 weeks premating, mating through day 7 of gestation
Segment II (rabbits)	C. Implantation to closure of hard palate D. Closure of hard palate to the end of pregnancy	Embryo-fetal development	Females: Day 6 to day 20 of pregnancy

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

- 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).

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

In a recent article, Ohno (1999) discussed not the harmonization of nonclinical guidelines but 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 women in such trials is becoming more important and, therefore, evaluation of embryo-fetal development should occur earlier in the drug development process than in Japan. Whether such timing or staging of nonclinical tests becomes part of an ICH guideline in the near future remains to be established.

Other International Considerations

The United States is the single largest pharmaceutical market in the world. But the rest of the world 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 it certainly has not obliterated these differences. Though a detailed understanding of their regulatory schemes is beyond this volume, the bare bones and differences in toxicology requirements are not.

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
  - 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.

Japan

In Japan, the Koseisho is the national regulatory body for new drugs. The standard LD50 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 causes 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 (again, rabbit is 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, 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 is 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 also 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

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

Duration of Dosing in Toxicity Study	Duration of Human Exposure
1 Month	Single dose or repeated dosage not exceeding 1 week
3 Months	Repeated dosing exceeding 1 week and to a maximum of 4 weeks
6 Months	Repeated dosing exceeding 4 weeks and to a maximum of 6 months
12 Months[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, *Expedited Programs for Serious Conditions—Drugs and Biologics*. CDER & CBER, Silver Spring, MD, 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf (Accessed November 16, 2015); ICH, *International Conference on Harmonization Safety Steps 4/5 Documents*. Interpharm Press, Buffalo Grove, IL, 1997.

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

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, 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.

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 (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. However, the trend in the United States and the EU toward including women earlier in the critical program has not yet been embraced in Japan.

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.

Safety Pharmacology

Japan was the first major country to require 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 the 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.

Even with harmonization as per the ICH, there remains significant variations over the length of the entire process that takes a drug through to market (Hirako et al., 2007; Gad, 2011, 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, or CTD) for worldwide regulatory submissions (see Table 2.17 for an outline of components) has been a huge step for global harmonization.

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

COMBINATION PRODUCTS

Recent years have seen a vast increase in the number of new therapeutic products that 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 devices 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):

1. 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.
2. Registration and listing under Section 510, including some CDER-administered device applications. CDER will receive printouts and other assistance, as requested.
3. Color additives under Section 706, with review by CDER, as appropriate.
4. GMPs Advisory Committee. Under Section 520(f) (3), CDER will regularly receive notices of all meetings, with participation by CDER, as appropriate.
5. 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.

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, 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.

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3 Animal Health Products

Elizabeth Roberts

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From a regulatory perspective, veterinary animal health products are divided into two groups: those given to companion animals (pets) and those administered to food-producing animals. The safety assessment and regulatory focus for each group are unique. This chapter outlines the steps required to bring these veterinary products to market in the United States (US). Regulations governing veterinary products, as well as the organization of the Food and Drug Administration's Center for Veterinary Medicine (CVM) are presented. Available CVM guidance for direction in planning, executing, and submitting studies is listed. The components of the initial filing of an Investigational New Animal Drug Application (INAD) and the organization and contents of the New Animal Drug Application (NADA) are discussed. Finally the risk assessment process, international considerations in veterinary product development, and off-label use are presented.

CENTER FOR VETERINARY MEDICINE

Regulatory History

Under the federal Food, Drug, and Cosmetic Act, the Center for Veterinary Medicine of the US Food and Drug Administration (US FDA or FDA) is responsible for reviewing, evaluating, and approving all drug products for use in animals prior to introducing the drugs into the marketplace.

Massachusetts enacted the first food law in the US in 1784, but the first attempt to control animal health occurred in 1891 when Congress passed an act requiring the inspection of animals for disease prior to slaughter.

Dr. Harvey Wiley was appointed chief chemist, US Department of Agriculture (USDA) in 1883 and is credited with establishing the regulation of foods and drugs. His efforts resulted in the enactment of the first Food and Drug Act ("the Act") in 1906. In 1927, responsibility for enforcement of the Food and Drug Act was given to the newly established FDA. (The Agency was first called the Food, Drug, and Insecticide Administration and was given its current name in 1930.) The Act was extended in 1938 to cover cosmetics and medical devices and required all drugs to be shown safe for use. Additional amendments, such as for food color additives, were added. These include the Kefauver–Harris Amendment (1962), requiring that all drugs be shown to be both safe and effective prior to distribution and sale, that drug advertising disclose accurate information about side effects, and that generic drugs are prohibited from being marketed as new *breakthrough* medications. This amendment contained a clause (the Delaney Clause, also termed the *DES exemption*) permitting the use of potentially cancer-causing drugs in production animals provided that no detectable levels of residue are found in the human food supply. Pesticide use was removed from the Delaney Clause in 1996 by an amendment to Title IV of the Food Quality Protection Act (FQPA). The FQPA standardized the way the Environmental Protection Agency (EPA) would manage the use of pesticides and amended the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act. It mandated a health-based standard for pesticides used in foods, provided special protections for babies and infants, streamlined the approval of safe pesticides, established incentives for the creation of safer pesticides, and required that pesticide registrations remain current. In 2004 the Minor Use and Minor Species Animal Health Act was passed to encourage the development of veterinary therapies for species that would otherwise attract little interest and to discover treatments for medical conditions of relatively low prevalence in the major species identified as cattle, horses, swine, chickens, turkeys, dogs, and cats.

Organization and Administration

The CVM is one half of the FDA's Office of Foods and Veterinary Medicine. Along with the Office of the Director, the CVM is comprised of five additional offices—Management, New Animal Drug Evaluation, Surveillance and Compliance, Research, and Minor Use and Minor Species. The office of primary interest to toxicologists involved in veterinary product development is that of the Office of New Animal Drug Evaluation (ONADE). This is divided into eight divisions, each charged with the evaluation or oversight of different aspects of the new animal drug review process. Effectiveness and target animal safety evaluation are the responsibility of two divisions, which evaluate drugs for therapeutic use in both food animals and non-food animals; one division which evaluates the use of agents in agricultural production; and one division which evaluates generic animal drugs. The division of human food safety evaluates the safety to the public by ensuring edible products derived from food-producing animals treated with new animal drugs are safe for human consumption. The division of manufacturing technologies evaluates the manufacturing processes and quality control. The division of scientific support evaluates the environmental impact and provides statistical and clinical pharmacology support across all the scientific review divisions. And to ensure ONADE operates in an efficient and effective manner, one division provides business informatics, project management, quality assurance, and records management support. A current listing of the organization, including the personnel in each division and their contact information, can be obtained from the CVM by written request or at the CVM website (http://www.fda.gov/AnimalVeterinary).

The Code of Federal Regulations (CFR) is published by the Office of the Federal Register, National Archives and Records Administration as a special edition of the Federal Register and is

available for purchase from the Superintendent of Documents, US Government Printing Office, Washington, DC 20402. CFR Title 21 includes the volumes pertaining to the FDA, which are updated each year effective April 1. Title 21, Parts 500–599 include regulations governing animal drugs, animal feed, and related products. Requirements such as registration, listing, labeling, and current Good Manufacturing Practices (GMPs) are contained in Title 21, Parts 200–299. Good Laboratory Practice (GLP) for Nonclinical Studies is listed in 21 CFR 58.

For help in understanding these laws and regulations, the CVM makes available a series of educational materials to assist toxicologists, veterinarians, and individuals in the animal drug and feed industries. These materials can be acquired from the CVM website (http://www.fda.gov/cvm), through the CVM Industry Information Staff at The Center for Veterinary Medicine, Communications, and Education Branch, 7500 Standish Place, HFV-12, Rockville, MD 20855 (phone: 301-594-1755). Additional information can be obtained from the CVM's Office of New Animal Drug Evaluation, HFV-100, 7500 Standish Place, Rockville, MD 20855 (phone: 301-594-1620, fax: 301-594-2297).

The Center for Veterinary Medicine Memos (CVMMs), published by the Agency, are intended to help industry, scientists, veterinary professionals, and the general public better understand the laws and regulations enforced by the FDA and to improve the safety and effectiveness of animal drugs. The Center for Veterinary Medicine Memos are available from the FDA Industry Information Staff.

In addition to the regulatory guidance provided by the CVM, the US, European Union (EU), and Japan have strived to harmonize the requirements for pharmaceutical development. Most of the guidelines for veterinary pharmaceutical development follow the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) launched in April 1996. The objective of VICH is to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for the authorization of medicines. These guidances provide recommended procedures for collecting research data necessary to support new animal drug approval requirements. While these guidelines describe procedures acceptable to the FDA, they do not preclude alternative methods, provided that the drug sponsor believes other methods may be applicable. Discussion with the CVM *prior* to undertaking studies is advisable. A listing of pertinent guidances that may be helpful can be found at the end of this chapter.

Freedom of Information

In addition to CVMMs and guidance documents that are usually available at no cost and accessible on the internet, the Freedom of Information Act permits an individual or corporation to procure a "Freedom of Information (FOI) Summary" of an approved drug. This document can be requested online at http://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm or in writing from the FDA Division of Freedom of Information, Office of the Executive Secretariat, OC, 5630 Fishers Lane, Room 1035, Rockville, MD 20857. This can also be acquired through private companies, such as FOI Services, Inc. (704 Quince Orchard Road, Suite 275, Gaithersburg, MD 20878-1703), which typically charge a fee for this service. Requests directed to the FDA are published in the Freedom of Information Log, which is available to the public. The request for a drug FOI Summary should contain the trade name, generic name (if applicable), and manufacturer, and it must contain the following statement: "Under the Freedom of Information Act and implementing regulations, please forward to us the following..."

The FOI Summary for a drug is initially drafted by the sponsor and reviewed and approved by the CVM as a required part of the New Animal Drug Application or the abbreviated New Animal Drug Application (ANADA). The summary is released for public view and made available for distribution when the drug is approved. The FOI document must provide a summary of each study performed to gain approval in sufficient detail to demonstrate the safety and effectiveness of the drug.

Corroborative or supportive (non-pivotal) studies are generally not included in the FOI document. For example, an FOI Summary may contain the following elements:

- *General information*: NADA number, sponsor, product name, pharmacological category, dosage form, how supplied, dosage, route of administration, species, indications for use
- *Effectiveness*: The dose rationale, including studies conducted to establish a dose or a dose range; clinical study summaries providing substantial evidence of effectiveness and field safety
- *Target animal safety*: Pivotal study summaries including data from target animal safety studies and reproductive safety studies (if the product is to be used in breeding animals)
- *Human food safety*: Establishment of tissue tolerance levels, as well as withdrawal times following treatment, in animals intended for food
- *User safety*: Information regarding safety to humans including information on the handling, administration, or exposure to the drug product
- *Agency conclusions*: Final section of a NADA left blank by the sponsor; the Agency places its conclusion here
- *Attachments*: Include labeling for all packaging (including samples), the finding of *no significant environmental impact* and supporting Environmental Assessment

Animal Drug User Fee Act

The Animal Drug User Fee Act of 2003 (ADUFA), amended the Federal Food, Drug, and Cosmetic Act (FFDCA) and authorized the FDA to collect fees for certain animal drug applications, and for the establishments, products, and sponsors associated with these and previously approved animal drug applications, in support of the review of animal drugs. The ADUFA, originally passed in 2003, was set to expire September 2008. On August 14, 2008, the Animal Drug User Fee Amendments of 2008 (also referred to as ADUFA II) was signed. The amendments extended ADUFA until 2013. On June 13, 2013, the Animal Drug and Animal Generic Drug User Fee Reauthorization Act of 2013 (also referred to as ADUFA III) was signed, reauthorizing ADUFA. This most recent reauthorization extends ADUFA until 2018.

The ADUFA III reauthorization maintained the review timeframes identified in 2008 for key submissions in addition to adding certain revisions to the program (Table 3.1).

TABLE 3.1
Timeframes Outlined in ADUFA 2008 and Maintained in ADUFA III[a]

Submission Type	Timeframe in Days after Submission Date
Animal drug applications (NADAs) and reactivations of such applications	180
Non-manufacturing supplemental animal drug applications (i.e., supplemental animal drug applications for which safety or effectiveness data are required) and reactivations of such supplemental applications	180
Manufacturing supplemental animal drug applications and reactivations of such supplemental applications	120
Investigational animal drug study submissions	180
Investigational animal drug submissions consisting of protocols, that the Agency and the sponsor consider to be an essential part of the basis for making the decision to approve or not approve an animal drug application or supplemental animal drug applications	50
Administrative animal drug applications (NADAs submitted after all scientific decisions have been made in the investigational animal drug process—i.e., prior to the submission of the NADA)	60

[a] Agency agrees that 90% of the earlier submissions will be reviewed and acted upon within the prescribed timeframe.

Revisions in ADUFA III include: replacing the End Review Amendment (ERA) with a short second round review; reducing time for microbial food safety hazard characterization submissions to 100 days; adding a variable inflation adjustment to account for changes in the CVM's costs using the Consumer Price Index as a guide; and reducing the proportion provided by application fees from 25% to 20%. Additionally, there were Chemistry, Manufacturing, and Controls (CMC) changes including: permitting the manufacturing supplements to be resubmitted as "Supplement-Changes Being Effected in 30 Days" if deficiencies are not substantial for manufacturing supplements requiring prior approval according to 21 CFR 514.8(b); permitting comparability protocols as described in 21 CFR 514.8(b)(2)(v) to be submitted as protocols without substantial data in an INAD file; and developing guidance for a two-phased CMC technical section submission and review process under the INAD file.

REGULATORY PROCESS AND PROCEDURES

Open and early communication between the sponsor and the CVM is key in the successful development of a drug. The sponsor initiates this communication by contacting ONADE to open an INAD file and discuss the development plan for the new animal drug. The sponsor may first contact ONADE simply to discuss the best ways to share scientific information about a promising new animal drug (http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm).

Investigational New Animal Drugs

To initiate clinical field studies with a new animal drug, the drug must first be listed with the CVM as an Investigational New Animal Drug. The sponsor then uses this file as a way to correspond with the CVM throughout the drug development process. For example, the sponsor uses the INAD file to obtain an investigational withdrawal period to allow treated food-producing animals to enter the human food chain. (Without an established withdrawal period, production animals involved in clinical trials may not enter the food chain to be consumed by humans; in such cases, the carcasses must be destroyed. Depending on the compound and the available information, the CVM may grant an extended [conservative] withdrawal period for investigational use.) Also, the drug sponsor should notify the CVM before shipment of investigational drug products by submitting a "Notice of Claimed Exemption for an Investigational New Animal Drug" (21 CFR 511.1), along with a summary of known information about the drug. The intended use for the drug, the species in which it will be tested, a summary of available data and literature (including any foreign studies), and a summary of the toxicity testing performed to date with particular emphasis on the proposed target species should also be included. The exemption legally allows shipment of Investigational New Animal Drugs in interstate commerce for investigational use.

It is highly recommended that the sponsor meet with the CVM prior to development to clearly identify the regulatory approval requirements for the specific compound to be developed. The CVM strongly advises sponsors to submit protocols for planned pivotal efficacy and safety studies to the CVM for concurrence review prior to initiation of studies. The Agency will review the sponsor's proposals and may concur or issue further guidance for protocol amendment—the aim being to reach agreement *a priori*, fundamentally agreeing with the design, execution, and analyses proposed in the protocol. Concurrence represents a commitment that the CVM will not later alter perspectives on discussed and agreed upon issues unless public or animal health concerns appear that were not recognized at the time of the protocol assessment. However, the CVM protocol concurrence does not guarantee that the data obtained from a protocol concurred study will support an approval. In addition, concurrence does not extend to any subsequent changes made to the protocol; the CVM recommends additional concurrence on any revisions.

Components of the Approval Process

Initially the sponsor has to determine the dosage form of the drug and the dosage regimen (dose, frequency, duration of treatment, route of administration) believed to be the most appropriate. Examples of the dosage form include oral (tablets, capsules, etc.) or injectable (subcutaneous, intramuscular, or intravenous) formulas. Data must be presented for a dose rationale, termed *dosage characterization*. These data may be from traditional dose titration testing or from other target animal studies in which a dose response is demonstrated and a basis established for the proposed therapeutic dose.

There are five major technical sections:

- Effectiveness
- Target animal safety
- Human food safety
- Chemistry, manufacturing, and controls
- Environmental impact

1. *Effectiveness*: The sponsor must show that the drug works in the target animal species when used according to the label. This is generally accomplished through clinical testing performed in the field in client-owned animals by qualified investigators (usually licensed, practicing veterinarians who have an established veterinary client-patient relationship) selected by the drug sponsor. At least one well-controlled pivotal clinical study must be submitted. The number of animals per test group should be statistically determined using sample size calculations. Ideally, clinical studies should be performed according to VICH GL9 Good Clinical Practice (GCP) in geographically separate areas of the United States to demonstrate that the drug is efficacious and safe in a variety of different situations.
2. *Target animal safety*: The drug sponsor must also show that the drug is safe in the target animal species when used according to the label. To prove the drug's safety, the sponsor typically conducts a target animal safety study in a small number of healthy animals. The goals of a standard target animal safety study are:
   - To identify any harmful side effects of the drug.
   - To establish a margin of safety for the drug (This is usually determined by testing the drug at higher-than-labeled doses for a longer-than-labeled time period in the target animal species. The drug's margin of safety is to ensure the drug will be safe when used in animals that may be sick or sensitive to the drug.).
3. *Human food safety*: Drug resistance in people and animals is a growing public health concern, particularly resistance to antibiotics. Antibiotic-resistant bacteria that enter the food supply may add to drug resistance in people. Food products made from treated animals must be safe for people to eat. To show that the food products are safe, a sponsor usually conducts human food safety studies to make sure the level of chemical residues in or on food made from treated animals will not harm people and to minimize the number of antibiotic-resistant bacteria that enter the food supply in or on food products made from treated animals.
4. *Chemistry, manufacturing, and controls (CMC)*: In the CMC technical section, the sponsor describes the plan for making the drug. The CVM works with the sponsor to design a testing plan, including an FDA inspection of the manufacturing facilities to make sure the methods and equipment used will consistently produce a high-quality and safe drug.
5. *Environmental impact*: Under the National Environmental Policy Act (NEPA), the CVM must consider how the environment will be affected by an animal drug after it is approved. This requires the sponsor to prepare an Environmental Assessment (EA). An EA describes how much drug is expected to get into the environment and its potential effects. If the

CVM decides that the drug will not have a significant impact on the environment based on the information in the EA, the Agency concludes a *Finding of No Significant Impact*, or *FONSI* for short. If the CVM decides that the drug will have a significant environmental impact, an Environmental Impact Statement (EIS) is needed. Refer to the following website for more information on environmental impact considerations: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm.

A sponsor may ask the CVM for a waiver from having to prepare an EA. This waiver is called a *Categorical Exclusion*, or *CE* for short. A CE indicates that the drug falls into a legally-defined category that is unlikely to cause a significant environmental impact. If the Agency grants a CE, the sponsor does not have to prepare an EA.

There are also two minor technical sections:

1. *All other Information*: Includes all information about the drug that was not part of the five major technical sections. The sponsor typically collects this information from such sources as published scientific literature, foreign experience (if the drug is approved in a country outside the US), medical experience in people (if the drug is approved for use in people), and any studies that were conducted by the sponsor but not included in the five major technical sections.
2. *Labeling*: Includes all information on the immediate container, package insert, outer package, shipping label, and when needed, the client information sheet.

NEW DRUGS

The Agency permits either a phased review process where each major technical section may be submitted individually or all sections submitted as one submission. Typically, a sponsor will elect a phased review. Either approach will conclude with an administrative NADA for approval.

New Animal Drug Application

General

Section 512(b)(1) of the FFDCA sets forth the broad requirements for the content of a NADA. Section 512(c) of the FFDCA requires the FDA to take an appropriate action within 180 days after the filing of a NADA (or an ANADA).

Sections of the New Animal Drug Application

21 CFR 514.1 provides the outline for the organization and content of a NADA for both paper and electronic submissions. The NADA contains the following sections:

1. *Identification*: This section defines the NADA. Form FDA 356V (for paper submissions only) and a cover letter are included.
2. *Table of contents and summary*: A detailed table of contents is presented to allow the various FDA reviewers easy access to information in the NADA. The summary is concise, yet contains all the salient points that need to be highlighted for the reviewers.
3. *Labeling*: A copy of the sponsor's draft label for the product is required. A request to the CVM for a label from a product that has been approved recently may be helpful in formatting the label according to current FDA style.
4. *Components and composition*: A complete list of articles used for production of the new animal drug and a full list of each article used in the composition of the drug product should be provided.

5. *Manufacturing information*: This section contains a complete description of the facilities, equipment, and manufacturing procedures used to prepare the drug substance and finished dosage form.
6. *Drug samples*: Reference samples of the drug and a sample of the finished dosage form are to be submitted on request.
7. *Residue information*: Toxicology data required to establish human safety are presented, if required, and residue information, including analytical methods for the residues, is detailed for drugs indicated for production animals.
8. *Safety and efficacy*: Target animal safety data, toxicity data, and the results of clinical field trials are presented. Compatibility studies with other drugs may be required. If the drug is an antibiotic for use in food-producing animals, microbial resistance and Salmonella shedding studies may be necessary.
9. *Good laboratory practices*: A statement of compliance or non-compliance with good laboratory practices is presented for each safety study.
10. *Environmental impact*: This section details the environmental studies conducted with the product. The effect of the drug on the environment is based on estimated sales and use patterns of the drug and the residence time of the drug in the environment. Categorical exclusion may be requested in some cases, excepting the need to provide an Environmental Assessment (21 CFR 25.33 (a), (c), (d), or (e)).
11. *Freedom of information summary*: The FOI summary is drafted by the sponsor, reviewed and accepted by the CVM, and supplied to the public upon request.

Supplements and Amendments

Supplements or amendments to the NADA should contain only the sections that apply. The CVM no longer requires supplemental applications for minor changes, such as extension or expiration dates, updates in specifications or methods to bring them into compliance with official methods, or minor label changes. The notification necessary for various changes is provided in 21 CFR 514.8.

GENERIC DRUGS

Abbreviated New Animal Drug Application

In 1988, the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) amended the FFDCA to provide for the approval of generic copies of new animal drug products that have been previously approved and shown to be safe and effective when used according to their labeling. It also requires that NADAs contain patent numbers and expiration dates of patents covering each component of the application. Bioequivalence of generic versions of drugs against the FDA-designated reference product must be established. For true solutions, and for some topical products, the need to conduct animal bioequivalence studies may be waived. Animal drug pharmacokinetic studies, pharmacologic end-point studies, or clinical end-point studies are required to establish bioequivalence for the filing of an ANADA.

Bioequivalence is preferably demonstrated through studies that determine the concentration of the parent compound(s) and/or metabolite(s) in serum or plasma following the administration of the drug product. If a blood level study is not feasible (e.g., when a satisfactory analytical method is not available), a physiological end-point study may be substituted. Clinical end-point studies, in which improvement in a disease state (e.g., parasite burden) is measured may also be acceptable for some drugs, such as anthelmintic products. For drugs used in food-producing animals, the FDA requires tissue residue depletion studies in addition to blood level or end-point equivalence studies.

In 2008, the Animal Generic Drug User Fee Act (AGDUFA) established a *user fee* system similar to the system for brand name animal drugs. The AGDUFA authorizes the CVM to collect fees from sponsors to support the CVM's review of generic animal drugs.

More information concerning GADPTRA and AGDUFA can be found at the following websites:

- http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/ActsRulesRegulations/ucm049100.htm
- http://www.fda.gov/ForIndustry/UserFees/AnimalGenericDrugUserFeeActAGDUFA/default.htm

ELECTRONIC SUBMISSIONS

The FDA's part 11 regulations (21 CFR 11) establish the criteria under which records submitted to the FDA may be submitted in electronic format in place of paper. Section 11.2(b) states that, for records submitted to the Agency, persons may use electronic records in lieu of paper records. While paper submissions are still considered acceptable, the Agency now prefers electronic submissions and encourages sponsors to submit electronically.

On March 11, 2011, the CVM released an electronic submission tool, eSubmitter, for use in submitting INAD and NADA submissions. Electronic submission eliminates the need for paper, reduces printing and mailing costs, and allows the CVM to review submissions electronically. The development and release of eSubmitter also meets one of the goals of the 2008 ADUFA, which required the creation of a tool for INAD and NADA electronic submissions. The CVM expanded the development of the electronic tool to include all submission types. Along with the INAD and NADA submissions, eSubmitter permits the creation and submission of Generic Investigational New Animal Drug (JINAD) files, ANADA applications, Veterinary Master Files (VMF), and General Correspondence (GC) files.

The FDA eSubmitter is a *free software* that supports the creation of electronic submissions. The software and any output files reside locally on personal computers. The eSubmitter tool does not transmit data across the internet to the FDA. Once a submission is packaged in eSubmitter, it can then be securely submitted through the FDA's Electronic Submissions Gateway (ESG). Anyone transmitting electronic submissions to the CVM must first register with the FDA Gateway and follow all requirements for setting up an account. Following the establishment of an FDA ESG account, individuals must register with the CVM and follow the requirements in the Guidance for Industry #108 How to Submit Information in Electronic Format to CVM using the FDA Electronic Submission Gateway.

For additional information or to download and install eSubmitter, please refer to http://www.fda.gov/ForIndustry/FDAeSubmitter/ucm226814.htm. Questions about the CVM's eSubmitter program can be emailed to the CVM eSubmitter team at cvmesubmitter@fda.hhs.gov.

For ESG-related questions, send email to ESGHelpDesk@fda.hhs.gov.

RISK ASSESSMENT

Risk assessment for animal health products includes an assessment of risk to the target animal, the environment, the drug handler, and the human consumer relative to drug residues in meat, milk, and eggs.

Target Animal Safety

Risk to the target animal species is addressed with target animal safety (TAS) studies and demonstrated safety in the field. Target animal safety guidances have been established for dogs, cats, horses, ruminants, swine, and poultry (see the CVM guidance and VICH GL43). These guidances detail how to design an acceptable protocol. Studies must be performed at one, three, and five times

(1x, 3x, 5x) the proposed clinical dose for three times the proposed duration of use (for chronic medications to be used in dogs and cats—such as diuretics or cardiac drugs—studies of six months or longer may be needed). Therefore, the conduct of definitive safety studies is not possible until after the establishment of a dose. The sponsor should evaluate the likelihood of toxicity with a short-term study to decide whether a drug tolerance study will be needed. A negative control group (untreated, placebo, or vehicle) must be included in all target animal safety studies. The number of animals per group for target animal safety studies will depend on the investigational drug and the intended target species. Refer to the current CVM guideline for the specific target animals.

If signs and symptoms of toxicity are observed in the TAS study, a separate drug tolerance study may be needed. Historically, a drug tolerance test (performed as a single 10x dose) was performed to further demonstrate the drug's margin of safety. This may be appropriate, but its necessity should be addressed with the Agency.

If the drug is intended for use in breeding animals, reproductive safety testing in breeding animals is required. The goal of reproductive safety studies is to identify any adverse effects of the investigational product on male or female reproduction or on offspring viability. Requirements for reproductive studies are outlined in VICH Guideline 43. The parental, in utero, and postnatal exposure are adjusted to the specific target species and is dependent on the intended use of the drug. Ideally, reproductive safety studies are conducted in the target species; however, data obtained from reproductive studies in laboratory animals may be considered, provided that the pharmacokinetic profiles of the active pharmaceutical ingredient (API) are comparable in laboratory animals and in all species in which the investigational drug is intended for use. Depending on the results of such evaluation, appropriate information should be included on the labeling. However, if reproductive safety studies have not been conducted in the target species, labeling will reflect this and state that "safety has not been determined in breeding, pregnant, or lactating animals or their offspring."

Additional tests such as irritation studies for topical drugs or injection site tolerance studies should be performed if appropriate. Drug interaction studies with commonly used medications may be required in the target animal. These may include testing for interactions with commonly used food supplements or vitamins.

Environmental Assessment

For a drug used in food-producing animals, the risk to the environment and to the human handler of the product must be assessed. When an additive is administered to food producing animals in their feed, or when a dosage form is directly administered to animals either in a free-range situation or in a feedlot, the producer of such an additive or drug must calculate the potential effects on the environment. Drug and/or metabolites can reach soil, plants, and the water table through feedlot runoff, use of manure to fertilize crop fields, and by the raising of crops on pasture land.

The types of studies that should be conducted to prepare an environmental assessment report are described in detail in the Environmental Assessment Technical Handbook (National Technical Information Services, 5285 Port Royal Road. Springfield, VA 22161). These studies generally assess toxicity to wildlife, aquatic life, soil life, and plant life. The binding of drug to soil and its half-life in the environment must be calculated. This requires an assessment of photodegradation, hydrolysis, soil adsorption and desorption, and microbial breakdown of the drug and its major metabolites.

In addition to effects on the environment, when feed additives are prepared for inclusion in the diet of food-producing animals, the exposure to humans can be substantial. Most diet supplements are added to the animal feed at the farm or ranch where the animals are raised. The farmer who mixes the additive into the feed is not constrained by worker regulations, such as wearing protective clothing. Therefore, it is crucial to determine the effects of the product on humans who come in contact with the compound.

The risk for exposure to other species must also be considered for an animal feed additive that will be widely used on farms or ranches. When feeds are prepared for one species of animal, they

may also be inadvertently available to a different species. For example, horses, dogs, chickens, and cats may all be exposed to spilled cattle feed. Because species-specific toxicity may exist for these drugs, many of which are antibiotics, toxicity testing should be carried out in other species that have a high probability of ingesting feeds. For example, if toxicity testing indicated that horses were more sensitive to the drug than the target species, a distinctive warning label would need to be placed on the food additive container. Drugs available in medicated feed block form should also be tested for incidental consumption by other animals.

Human Food Safety

The major risk assessment effort connected with products for food-producing animals is the determination of the safe concentration of drug residues in edible tissues. This section of an application is most important and requires expert review. Refer to CVM GFI #3, which describes the type of information that the CVM recommends sponsors provide to address the human food safety of new animal drugs used in food-producing animals. Currently the guidance is in draft, where the revised guidance document is for comment purposes only and makes revision to the final guidance that was made available July 2006. The following is a summary of the current approach to establishing human food safety.

Human food safety is assessed through:

- *Toxicology*: Determination of the *acceptable daily intake* (ADI). The ADI is the largest amount of the drug that will not harm people if they ingest that amount every day.
- *Residue chemistry*: Using the ADI, the tolerance for the drug is set. Based on the tolerance, the withdrawal time is established. The withdrawal time is defined as the time required after administration of a drug to assure that drug residues in milk or meat is below a determined maximum residue limit (MRL).
- *Microbial food safety*: Determination of a drug's ability to cause bacteria to become resistant and the impact of any possible resistance on public health.

The drug sponsor must conduct the standard battery of short-term toxicity tests to determine the general food safety of the drug. These include three or more short-term genetic toxicity tests in two test systems, two subchronic feeding studies (usually in the rat and dog), and a multiple-generation reproduction study and teratology study in the rat. The sponsor thus determines the species most sensitive to the drug and establishes the *No Observed Effect Level* (NOEL) in mg/kg of body weight for that species.

Complete metabolism studies must be conducted, usually first in the target species, then in an experimental laboratory animal species. The purpose of the laboratory animal study is to demonstrate that the *surrogate* humans used in laboratory testing are exposed to the same metabolites as the human would be upon tissue (meat) ingestion. Most often it is necessary to use radio-labeled drug, preferably ^{14}C, to obtain the required level of detection in the various edible tissues of the production animal. Total residue of a chemical in treated animals consists of the unchanged parent compound, unbound free metabolites, and metabolites that are covalently bound to endogenous molecules. Different components of the total residue may have different toxicological potential. Therefore, the sponsor must generate data on the amount, persistence, and chemical nature of the total residue. Any residue consisting of 10% or more of the administered drug is usually considered significant and chemical identification of the residue is typically required by the FDA.

Conduct of studies in the target species must include consideration of the time required to reach steady-state conditions prior to establishing the drug residue depletion profile. Once steady-state is reached, sacrifices at several time intervals after drug administration establish the depletion of the drug from edible tissues and the identification of the target tissue, which is the edible tissue that contains the most drug or drug residue. This tissue will be used to monitor the drug should a withdrawal period be

necessary prior to marketing of the production animal. Further studies are required with the target tissue to establish which residue will be the marker compound for regulatory monitoring purposes.

Veterinary Feed Directive

The FDA amended the new animal drug regulations to implement the veterinary feed directive (VFD) drugs section of the Animal Drug Availability Act of 1996 (ADAA). On June 3, 2015, the FDA published in the Federal Register the final rule revising the VFD regulations in 21 CFR 558. The final rule became effective on October 1, 2015. In September of 2015, the FDA revised GFI #120 Veterinary Feed Directive Regulation to reflect the VFD final rule. A VFD drug is intended for use in animal feeds and such use of the VFD drug is permitted only under the professional supervision of a licensed veterinarian. The driving force for the initial VFD rule in 1996 and the recent revisions is to improve drug availability for the benefit of animal health and welfare and, in turn, food safety. The increasing threat of antibiotic resistance to both human and animal health compelled the FDA to take action by removing production uses of medically important antibiotics and implementing greater veterinary oversight by transitioning over-the-counter (OTC) antibiotics to VFD or prescription status. Effective January 1, 2017, all antimicrobials will be subject to the VFD.

INTERNATIONAL CONSIDERATIONS IN VETERINARY PRODUCT DEVELOPMENT

While there is a concerted effort to globally harmonize the requirements for pharmaceutical development, there remains a diversity of registration procedures across the world. Oftentimes, guidance and precedent for some veterinary medicines and/or regions are not available or, in some cases, registration is simply not possible. For example, in contrast to the US, the EU banned substances having a hormonal or thyrostatic action and beta agonists (Directive 96/22/EC, as amended by Directive 2008/97/EC). China has also banned the use of beta agonists and Brazil limits their use according to species. In addition, the EU has banned antimicrobial growth promoters (Regulation (EC) No 1831/2003) and substances prohibited for reasons of consumer safety (Regulation (EC) No 37/2010, Table 2).

Another example of an area with little regulatory guidance is that of biopharmaceutical products. There is recognition by the regulatory authorities that precedent set for similar molecules in human health may not be directly applicable to animal health, especially for an area that is still evolving. In this case, where good science remains paramount, seeking scientific advice from the regulatory authorities early in product development can enable the drafting of a relevant development plan.

Therefore, the regulatory climate in which a drug will be registered should be carefully monitored. In addition, individual country considerations may be very important for certain drug classes.

VETERINARY (OFF-LABEL) USE OF HUMAN PHARMACEUTICALS

Another potentially controversial issue is the off-label use of human drugs in animals. Human drugs are increasingly prescribed and dispensed to animal owners by veterinarians. Human drugs are used to treat companion animals with diseases for which there are no approved veterinary products. Economic considerations play a large role in the lack of development of specific veterinary products. Human drugs, even those for which there is specific animal information, may not contain any information on the label that suggests a use in animals, and the drug cannot be advertised for such uses, even to veterinarians. The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions. Extralabel use refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. Under AMDUCA and its implementing regulations published at 21 CFR 530, any extralabel use of an approved new animal or human drug must be by or on the lawful order of a veterinarian within the context of a veterinarian client-patient relationship (VCPR). Extralabel use must also comply with other provisions of 21 CFR 530. A list of drugs specifically prohibited from extralabel use appears in 21 CFR 530.41.

Relevant Guidance Documents and Guidelines

Center for Veterinary Medicine (CVM) Guidance for Industry

CVM GFI #3	General Principles for Evaluating the Safety of Compounds Used in Food Producing Animals
CVM GFI #5	Stability Guidelines
CVM GFI #6	Submitting NADA's for Generic Drugs Reviewed by NAS/NR
CVM GFI #13	Evaluation of Effectiveness of New Animal Drugs for Use in Free-Choice Feeds-Medicated Block
CVM GFI #23	Medicated Free Choice Feeds–Manufacturing Control
CVM GFI #24	Drug Combinations for Use in Animals
CVM GFI #35	Bioequivalence Guidance
CVM GFI #37	Evaluation of Effectiveness of New Animal Drugs for Use in Poultry Feed for Pigmentation
CVM GFI #38	Guideline for Effectiveness Evaluation of Topical/Otic Animal Drugs
CVM GFI #42	Animal Drug Manufacturing Guidelines-Series of Four Guidelines
CVM GFI #45	Guideline for Uniform Labeling of Drugs for Dairy and Beef Cattle
CVM GFI #49	Target Animal Safety and Drug Effectiveness Studies for Anti-Microbial Bovine Mastitis Products (Lactating and Non-Lactating Cow Products)
CVM GFI #50	Target Animal and Human Food Safety, Drug Efficacy, Environmental and Manufacturing Studies for Teat Antiseptic Products
CVM GFI #53	Evaluation of the Utility of Food Additives in Diet Fed to Aquatic Animals
CVM GFI #55	Supportive Data for Cat Food Labels Bearing Reduces Urinary pH Claims: Protocol Development
CVM GFI #56	Protocol Development Guideline for Clinical Effectiveness and Target Animal Safety Trials
CVM GFI #57	Preparation and Submission of Veterinary Master Files
CVM GFI #61	FDA Approval of New Animal Drugs for MUMS
CVM GFI #62	Consumer Directed Broadcast Advertisements
CVM GFI #65	Industry Supported Scientific and Educational Activities
CVM GFI #67	Small Entities Compliance Guide for Renderers
CVM GFI #68	Small Entities Compliance Guide for Protein Blenders, Feed Manufacturers, and Distributors
CVM GFI #69	Small Entities Compliance Guide for Feeders of Ruminant Animals with On-Farm Feed Mixing Operations
CVM GFI #70	Small Entities Compliance Guide for Feeders of Ruminant Animals Without On-Farm Feed Mixing Operations
CVM GFI #72	GMP'S For Medicated Feed Manufacturers Not Required to Register and be Licensed with FDA
CVM GFI #76	Questions and Answers BSE Feed Regulations
CVM GFI #79	Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by CVM
CVM GFI #80	Evaluation the Utility of Anti-Salmonella Chemical Food Additives
CVM GFI #82	Development of Supplemental Applications for Approved New Animal Drugs
CVM GFI #83	Chemistry, Manufacturing and Controls Changes to Approved NADA/ANADA
CVM GFI #98	Dioxin in Anti-Caking Agents in Animal Feed and Feed Ingredients
CVM GFI #102	Manufacture and Distribution of Unapproved Piperazine Products
CVM GFI #104	Content and Format of Effectiveness and Target Animal Safety Technical Sections and Final Study Reports for Submission
CVM GFI #106	Published Literature in Support of New Animal Drug Approval
CVM GFI #108	How to Register with the CVM Electronic Submission System
CVM GFI #118	Mass Spectrometry for Confirmation of Identity of Animal Drug Resides
CVM GFI #119	How CVM Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug
CVM GFI #120	Veterinary Feed Directive Regulation Questions and Answers
CVM GFI #122	Manufacture and Labeling of Raw Meat Foods for Companion and Captive Noncompanion Carnivores and Omnivores
CVM GFI #123	Development of Data Supporting Approval of NSAIDS for Use in Animal
CVM GFI #126	BACPAC I-Intermediates in Drug Substance Synthesis Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation

(*Continued*)

CVM GFI #132	Administrative Applications and the Phased Review Process
CVM GFI #135	Validation of Analytical Procedures for Type C Medicated Feeds
CVM GFI #136	Method Transfer Studies for Type C Medicated Feed Assay Methods
CVM GFI #137	Analytical Methods Description for Type C Medicated Feeds
CVM GFI #150	Concerns Related to the use of Clove Oil as an Anesthetic for Fish
CVM GFI #152	Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern
CVM GFI #156	Comparability Protocols—Chemistry, Manufacturing, and Controls Information for New Animal Drugs
CVM GFI #158	Use of Material from Deer and Elk in Animal Feed
CVM GFI #169	Drug Substance: Chemistry, Manufacturing, and Controls Information
CVM GFI #170	Animal Drug User Fees and Fee Waivers and Reductions
CVM GFI #171	Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles
CVM GFI #173	Animal Drug Sponsor Fees Under the Animal Drug User Fee Act (ADUFA)
CVM GFI #173	Appendix for the Animal Drug Sponsor Fees Under the (ADUFA)
CVM GFI #178	Design/Evaluation of Effectiveness Studies—Swine Respiratory Disease Claims
CVM GFI #179	Use of Animal Clones and Clone Progeny for Human Food/Animal Feed
CVM GFI #181	Blue Bird Medicated Feed Labels
CVM GFI #183	ADUFA-Animal Drug User Fees: Fees Exceed Costs Waiver/Reduction
CVM GFI #187	Regulation of Genetically Engineered Animals Containing Heritable Recombinant DNA Constructs
CVM GFI #188	Guidance for Data Elements for Submission of Veterinary Adverse Event Reports to the Center for Veterinary Medicine
CVM GFI #191	New NADAs vs. Category II Supplemental NADAs
CVM GFI #192	Anesthetics for Companion Animals
CVM GFI #195	Small Entities Compliance Guide for Renderers—Substances Prohibited From Use In Animal Food or Feed
CVM GFI #196	Process Validation: General Principles and Practices
CVM GFI #197	Documenting Statistical Analysis Programs and Data Files
CVM GFI #199	Animal Generic Drug User Fees and Fee Waivers and Reductions
CVM GFI #200	Small Entities Compliance Guide Designation of New Animal Drugs for Minor Uses/Minor Species
CVM GFI #201	SECG for Index of Legally Marketed Unapproved New Animal Drugs for Minor Species
CVM GFI #203	Ensuring Safety of Animal Feed Maintained and Fed On-Farm
CVM GFI #204	Active Controls in Studies to Demonstrate Effectiveness of a NAD for use in Companion Animals
CVM GFI #209	The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals
CVM GFI #211	Residual Solvents Q
CVM GFI #213	New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209
CVM GFI #215	Target Animal Safety and Effectiveness Protocol Development and Submission
CVM GFI #216	CMC Fermentation-Derived Intermediates, Drug Substances, and Related Drug Products for Veterinary Medicinal Use
CVM GFI #217	Effectiveness of Anticoccidial Drugs in Food-Producing Animals
CVM GFI #218	Cell-Based Products for Animal Use
CVM GFI #221	Recommendations for Preparation and Submission of Animal Food Additive Petitions
CVM GFI #223	Small Entity Compliance Guide Declaring Color Additives in Animal Foods
CVM GFI #226	Target Animal Safety Data Presentation and Statistical Analysis
CVM GFI #227	Two-Phased Chemistry, Manufacturing, and Controls (CMC) Technical Sections
CVM GFI #229	Evaluating the Effectiveness of New Animal Drugs for the Reduction of Pathogenic Shiga Toxin-Producing *E. coli* in Cattle
CVM GFI #230	Compounding Animal Drugs from Bulk Drug Substances
CVM GFI #231	Distributor Labeling for New Animal Drugs

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CVM GFI #232	VICH GL54 Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD)
CVM GFI #233	Veterinary Feed Directive Common Format Questions and Answers
CVM GFI #234	Question-Based Review for the Chemistry, Manufacturing, and Controls Technical Section of Animal Drug Applications
CVM GFI #237	Oncology Drugs for Companion Animals
CVM GFI #238	Modified Release Veterinary Parenteral Dosage Forms: Development, Evaluation, and Establishment of Specifications

Guidance for Industry (GFI)

GFI #103	Possible Dioxin/PCB Contamination of Drug and Biological Products
GFI #105	Computerized Systems Used in Clinical Investigations
GFI #112	Fumonisin Levels in Human Foods and Animal Feeds; Final Guidance
GFI #145	Bioanalytical Method Validation
GFI #151	FDA Export Certificates
GFI #220	Use of Nanomaterials in Food for Animals

Veterinary International Conference on Harmonization (VICH) Guidelines

VICH GL1	Validation of Analytical Procedures: Definition and Terminology
VICH GL2	Validation of Analytical Procedures: Methodology: Final Guidance
VICH GL3(R)	Stability Testing of New Veterinary Drug Substances
VICH GL4	Stability Testing of New Veterinary Dosage Forms
VICH GL5	Stability Testing-Photostability Testing of New Veterinary Drug Substances and Medicinal Products
VICH GL6	EIA's for Veterinary Medicinal Products—Phase I
VICH GL7	Effectiveness of Anthelmintics: General Recommendations
VICH GL8	Harmonisation of Technical Requirements for Approval of Veterinary Medicinal Products on Stability Testing for Medicated Premixes
VICH GL9	Good Clinical Practice
VICH GL10(R)	Impurities In New Veterinary Drug Substances
VICH GL11(R)	Impurities in New Veterinary Medicinal Products
VICH GL12	Efficacy of Anthelmintics: Specific Recommendations for Bovines
VICH GL13	Efficacy of Anthelmintics: Specific Recommendations for Ovines
VICH GL14	Efficacy of Anthelmintics: Specific Recommendations for Caprines
VICH GL15	Specific Recommendations for Equine
VICH GL16	Specific Recommendations for Porcine
VICH GL17	Testing of New Biotechnological/Biological Products
VICH GL18	Residual Solvents in New Veterinary Medicinal Products
VICH GL19	Specific Recommendations for Canine
VICH GL20	Specific Recommendations for Feline
VICH GL21	Specific Recommendations for Poultry-Gallus Gallus
VICH GL22	Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Studies
VICH GL23	Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing
VICH GL24	Management of Adverse Event Reports (AER's)
VICH GL27	Pre-Approval for Registration of New VMPs for Food-Producing Animals to Antimicrobial Resistance
VICH GL28	Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Carcinogenicity Testing
VICH GL29	Pharmacovigilance of Veterinary Medicinal Products: Management of Periodic Summary Update Reports (PSUs)
VICH GL30	Pharmacovigilance of Veterinary Medicinal Products: Controlled List of Terms
VICH GL31	Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food Repeat Dose (90 Day) Toxicity Testing
VICH GL32	Developmental Toxicity Testing
VICH GL33	Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing
VICH GL35	Pharmacovigilance of Veterinary Medicinal Products Electronic Standards for Transfer of Data

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VICH GL36	Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI
VICH GL37	Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing
VICH GL38	EIA's for Veterinary Medicinal Products, Phase II
VICH GL39	Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances
VICH GL40	Test Procedures/Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Product
VICH GL43	Target Animal Safety for Veterinary Pharmaceutical Products
VICH GL45	Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products
VICH GL46	Metabolism Study to Determine the Quantity and Identify the Nature of Residues
VICH GL47	Comparative Metabolism Studies in Laboratory Animals
VICH GL48	Marker Residue Depletion Studies to Establish Product Withdrawal Periods
VICH GL49	Validation of Analytical Methods Used in Residue Depletion Studies
VICH GL51	Statistical Evaluation of Stability Data
VICH GL52	Bioequivalence: Blood Level Bioequivalence Study
VICH GL53	Electronic Exchange of Documents: File Format Recommendations

Other

FDA's Strategy on Antimicrobial Resistance—Questions and Answers

Supplement to VICH GL52—Supplemental Examples, for Illustrating Statistical Concepts Described in the VICH In Vivo Bioequivalence Draft Guidance GL52

4 Regulatory Aspects and Strategy in Medical Device and Biomaterials Safety Evaluation

Shayne C. Gad

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In the United States (according to 201(h) of the Food, Drug, and Cosmetic Act), a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component, part, or accessory that is

- Recognized in the official National Formulary, the US Pharmacopoeia (USP), or any supplement to them.
- Intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body or man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals, and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes (CDRH, 1992).

While there are some unusual exceptions (e.g., imaging and contrast agents, which in both the US and EU are classified and regulated as drugs), this same operational definition generally applies across the major global markets.

REGULATORY BASIS

Regulations: General Considerations for United States

The US regulations for medical devices derive from seven principal laws:

1. Federal Food, Drug, and Cosmetic Act of 1938
2. Medical Device Amendments of 1976
3. Safe Medical Devices Act of 1990
4. Medical Device Amendments of 1992
5. FDA Modernization Act of 1997 (Section 204)
6. Blue Book Memos—ODE Guidance Memoranda of 1997
7. Use of International Standard ISO-10993 (2013)

The U.S. federal regulations that govern the testing, manufacture, and sale of pharmaceutical agents and medical devices are covered in Chapter 1, Title 21, of the Code of Federal Regulations (Hereinafter referred to as 21 CFR). Here 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 this arena would be Chapter 1, Subchapter A (Parts 1–78) of 21 CFR, which cover general provisions, organization, and so on. The good laboratory practices (GLPs) are codified in 21 CFR 58 (Gad, 2001). The regulations applicable to medical devices are covered in Subchapter H, Parts 800–895 of 21 CFR. As discussed earlier, the term medical device covers a wide variety of products: contact lenses, hearing aids, intrauterine contraceptive devices, syringes, catheters, drip bags, orthopedic prostheses, and so on. The current structure of the law was established by the Medical Device Amendment of 1976. Products on the market on the day the amendment was passed were assigned to one of three classes (I, II, or III), based on the recommendation of advisory panels. Medical device classification procedure is described in Part 860. Class I products (the least risk burdened) were those for which safety and effectiveness could be reasonably assured by general controls, such as devices available over the counter to the general public. Class II products were those for which a combination of general controls and performance standards were required to reasonably assure safety and effectiveness. Class II devices are generally available only with a doctor's prescription but may be used at home. Class III products are those for which general controls and performance standards were inadequate; these were required to go through a premarket approval process. All devices commercially distributed after May 28, 1976 ("preamendment Class III devices"), which are not determined to be substantially equivalent to an existing marketed device, are automatically categorized as Class III and require the submission of a PMA. Please note that these are classifications for regulatory purposes only and are distinct from the classification (Health Industry Manufacturer's Association [HIMA]/Pharmaceutical Research and Manufacturers Association [PhRMA]) of product types (e.g., internal versus external) discussed elsewhere in this chapter. Kahan (1995) provided a detailed overview of what comprises general controls, performance standards and such.

There are, of course, standards and conventions to be followed in designing a safety package to support investigational device exemptions (IDEs), 510(k), or PMA, and these are discussed in a subsequent section of this chapter. The expansion and increased sophistication of ISO guidance's has tended to shift the balance towards an increasing set of required pre-IDE biocompatibility tests.

In order to obtain a license to market a device, a sponsor either submits a 510(k) premarket notification or applies for a Premarket Approval (PMA), as described in 21 CFR 814. Like an NDA, a PMA application is a very extensive and detailed document that must include, among other things, a summary of clinical laboratory studies submitted in the application 921 CFR 814.20(b)(3)(v)(A), as well as a section containing results of the nonclinical laboratory studies with the device, including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. As with drugs, these tests must be conducted in compliance with the GLP Regulations. Under the language of the law, a sponsor submits a PMA, which the FDA

then *files*. The acceptance for filing of an application means that "FDA has made a threshold determination that the application is sufficiently complete to permit substantive review." Reasons for refusal to file are listed in 814.44(e) and include items such as an application that is not complete and has insufficient justification for the omission(s) present. The agency has 45 days from receipt of an application to notify the sponsor as to whether or not the application has been filed. The FDA has 180 days after filing of a complete PMA (21 CFR 814,40) to send the applicant an approval order, an *approved* letter or a *not approved* letter, or an order denying approval. An *approval order* is self-explanatory and is issued if the agency finds no reason (as listed in 814.45) for denying approval. An *approved* letter 814.44(e) means the application substantially meets requirements, but some specific additional information is needed. A *not approved* letter, 814.45(f), means that the application contains false statements of fact, does not comply with labeling guidelines, or that nonclinical laboratory studies were not conducted according to GLPs, and so on. Essentially, an order denying approval means that the sponsor must do substantially more work and must submit a new application for PMA for the device in question. 510(k) premarket approval submissions are less extensive than PMAs but they still must include appropriate preclinical safety data 510(k)s and are supposed to be approved in 90 days.

An alternative is the "de novo" 510(k) route filed for devices for which there is a lack of a suitable predicate, but for which a determination of *no significant risk* has been made.

At the time of publication of the last edition of Regulatory Toxicology, actual review and approval times were much longer than the statutory limits. In 1995, the average total review time for Class III products in the United States cleared by 510(k) was 579 days (versus 240 days or less in the EU) (The Gray Sheet, 1996). As reported in the Fiscal Year (FY) 2017 Performance Report to Congress for the Medical Device User Fee Amendments, 95% of 510(k) Premarket Notifications met review-time goals in both FY2016 (with a goal of 130 days) and FY2017 (with a goal of 124 days) (FDA, 2018). See Chapter 1 for a discussion of general regulatory considerations (such as GLPs), which are applicable to all safety evaluation studies.

Organizations Regulating Device Safety in the United States

The agency formally charged with overseeing the safety of devices and diagnostics in the United States is the Center for Devices and Radiological Health (CDRH) of the FDA. It 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. Medical devices are specifically overseen by the CDRH, headed by a director. Drugs are overseen primarily by the Center for Drug Evaluation and Research (CDER) (though some therapeutic or health care entities are considered as biologically derived and therefore regulated by the Center for Biologics Evaluation and Research, or CBER). There are also *combination products* (part drug, part device) which may be regulated by either or both CDER/CBER and CDRH, depending on what the principal mode of action (PMOA) is determined to be by the FDA (CFR, 1992), as discussed in Chapter 14.

Classification of Devices

In the US, in accordance with the 1976 Medical Device Amendment, devices are categorized as follows.

- *Class I*: General Controls (equivalent to OTC)
- *Class II*: Performance Standards and Special Controls (distribution is licensed healthcare professional controlled)
- *Class III*: Premarket Approval (clinical use only)
- Preamendment Devices

In Europe, there is a lengthy set of rules in the EC Medical Device Directive (Council Directive, 1993) to place devices in Classes I, IIa, IIb, or III. Class I is the minimum grade and Class II the maximum. This classification determines the extent of supporting data that is required to obtain marketing approval.

In the USA, the FDA Center for Devices and Radiological Health recognizes three classes of medical device, and this system is based on whether the product was on the market prior to the passage of the 1976 Medical Device Amendments. If a new device is substantially equivalent to a preamendment device, then it will be classified the same as that device. This means that for Class I and II products, no premarket approval is necessary. Class III products need premarket approval, and all new devices that are not substantially equivalent to existing products fall automatically into Class III.

Japan (Ministry of Health, Labor and Welfare [MHLW]) and Korea have a somewhat different three class system. Class I includes products that have no body contact and would not cause any damage to the human body if they failed, for example, X-ray film. These products need to premarket approval in terms of medical device regulations, although they may need to be tested under industrial guidelines, like those of the OECD. Class II products have external contact with the body, Class III have internal contact, and both Class II and Class III need additional testing. Figure 4.1 presents the MHLW scheme for device classification.

Most of the regulatory interaction of a toxicologist involved in assessing the biocompatibility of devices is with the appropriate part of the CDRH, though for combination products the two centers charged with drugs or biologicals may also come into play. Within the CDRH there is a range of groups (called divisions) which focus on specific areas of use for devices (such as general and restorative devices; cardiovascular, respiratory, and neurological devices; ophthalmic devices; reproductive, abdominal, ear, nose, and throat, and radiological devices; and clinical laboratory devices). Within each of these there are engineers, chemists, pharmacologists/toxicologists, statisticians, and clinicians.

There is also at least one non-governmental body that must review and approve various aspects of devices, setting forth significant *guidance* for the evaluation of safety of devices. This is the United States Pharmacopoeia (USP), and its responsibilities and guidelines are presented later in this chapter.

The other two major regulatory organizations to be considered are the International Standards for Organization (ISO), with ISO 10993 standards (ISO, various dates), and the Japanese Ministry of Health and Welfare (MHW) with its guidelines (MHW, 1995).

BIOCOMPATIBILITY TESTING: MEDICAL DEVICES

In a statutory sense, historically, any item promoted for a medical purpose, which does not rely on chemical action to achieve its intended effect, is a medical device (as discussed earlier). *In vitro* diagnostic tests are also regulated as medical devices. The regulation of devices under these definitions has had a different history than that of drugs—it has not been as strict and has evolved at a slower rate. However, the requirements for the safety evaluation and biocompatibility evaluation of devices have rapidly been becoming more sophisticated and closer to evaluations required for new drugs. The safety concerns are, however, also somewhat different for medical devices. Toxicologic safety concerns for devices (as opposed to concerns of mechanical safety, such as disintegration of heart valves) are called biocompatibility concerns.

Medical devices are organized into three different classes and are regulated accordingly. Class III devices are subject to the greatest degree of regulation and include devices that are implanted in the body, support life, prevent health impairment, or present an unreasonable risk of illness or injury. These are subject to premarketing approval. Class II and Class I devices are subject to lesser control, required only to comply with general controls and performance standards.

There are several governing schemes for dictating what testing must be done on new Class III devices in the general case, with each developed and proposed by a different regulatory organization at different times over the last few years. ISO has attempted to harmonize these requirements so that different (or duplicate) testing would not need to be performed to gain device approval in different national markets. As discussed in the last chapter of this book, there are also specialized testing requirements for some device types such as contact lenses (FDA, 1997) and tampons (CDRH, 1995c). The ISO effort has generally been successful and parallels that of International Conference on Harmonization (ICH)

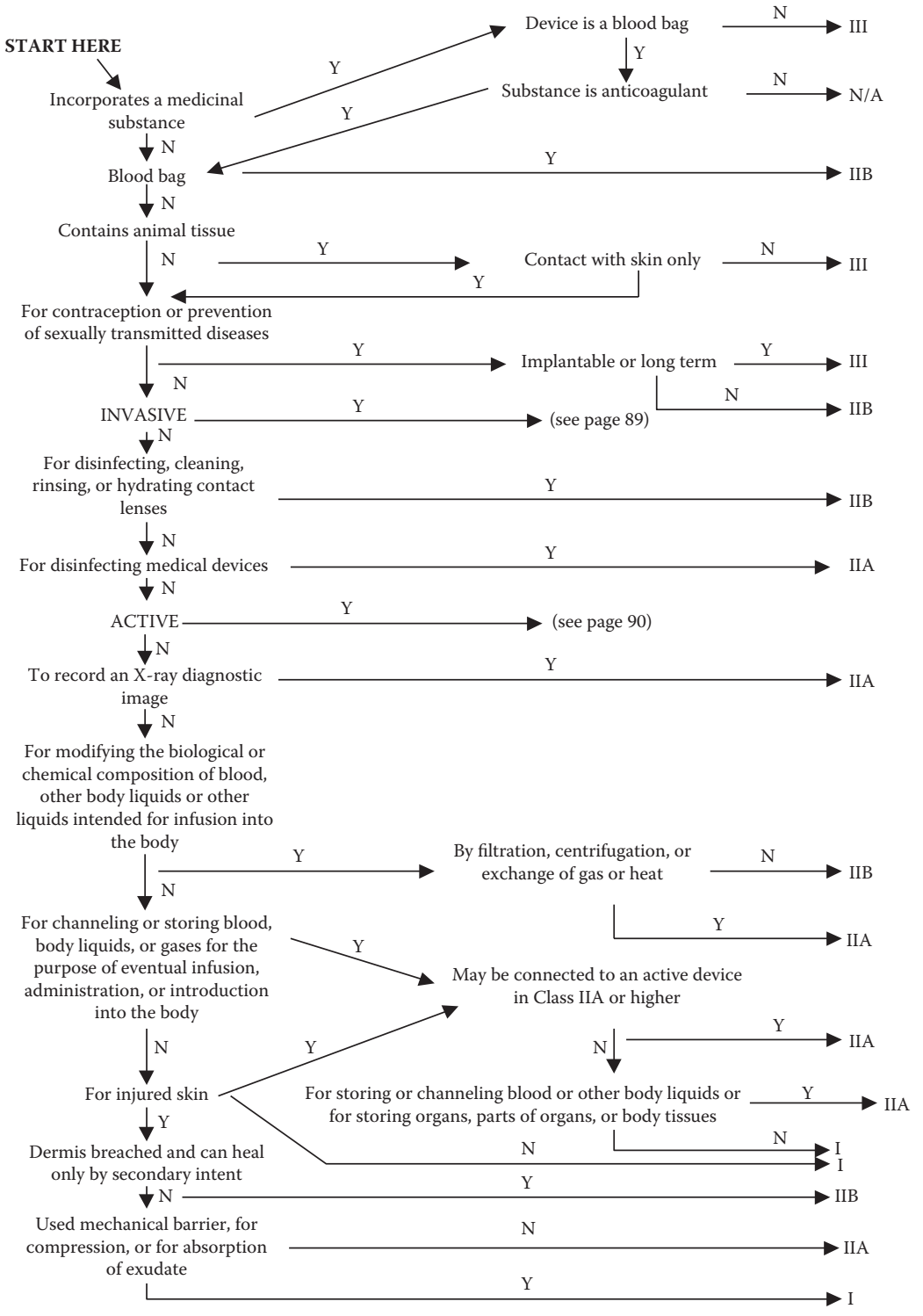

FIGURE 4.1 Medical device classification flowchart. (*Continued*)

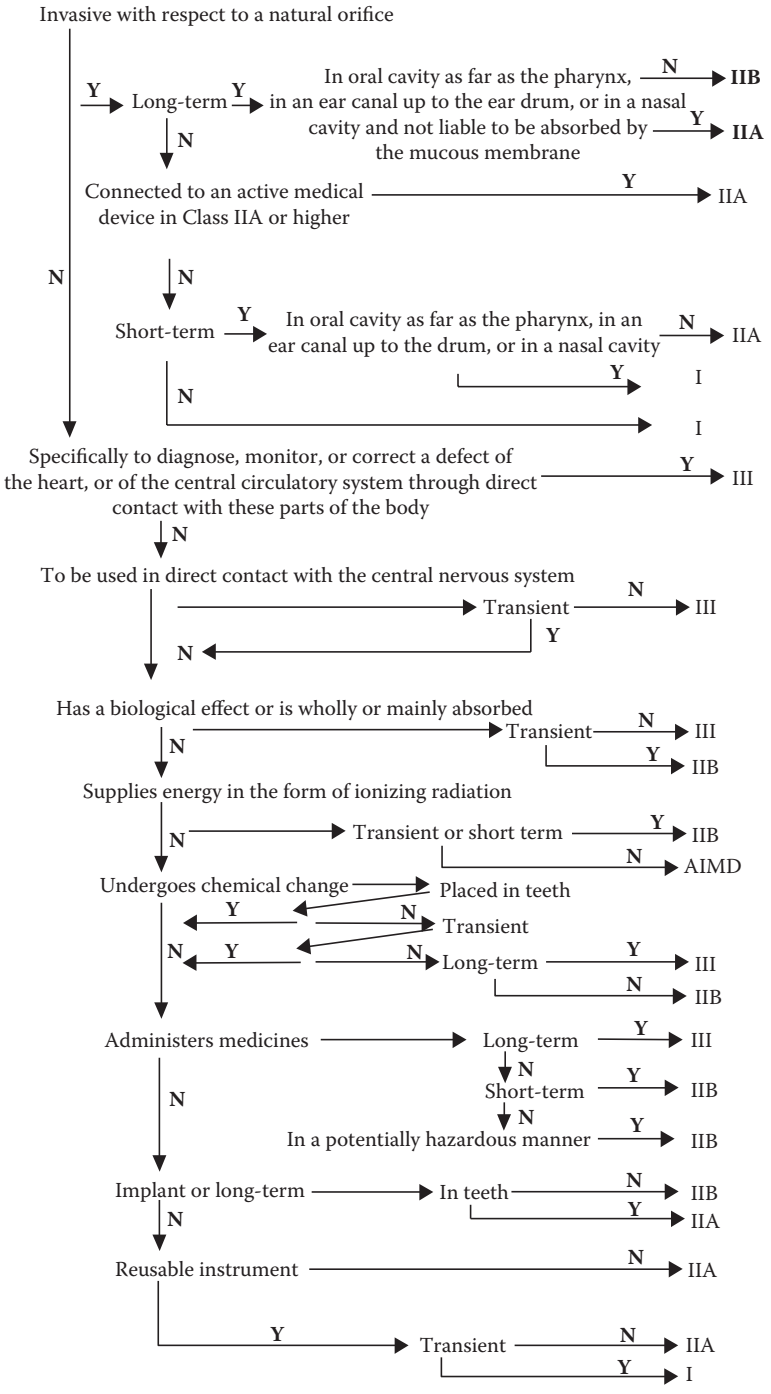

FIGURE 4.1 (Continued) Medical device classification flowchart.

for drugs (though ISO is, it should be noted, a non-governmental organization (NGO) and not a governmental regulatory body). Where differences exist, they are highlighted in this volume as specific requirements and designs are presented.

As with drugs, all safety testing for devices must be conducted in conformity with GLPs (FDA, 1987; Fries, 1999; Gad and Taulbee, 1996). Table 4.1 presents the existing FDA CDRH requirements

TABLE 4.1
Which Products Are Class I?

The Classification of a Product Refers to Its Intended Use. The Following Is a Simplified Listing of Class I Products:

- Noninvasive (and nonactive) devices that do not modify the biological or chemical composition of blood or liquids intended for infusion; store blood, body liquids, or tissues for administration; or connect to an active medical device.
- Dressings intended only as a mechanical barrier or for absorption of exudates.
- Invasive products for use in natural body orifices and stomas for no longer than one hour or in the oral or nasal cavity or ear canal for up to 30 days.
- Surgical invasive products if they are reusable instruments and not intended for continuous use of more than one hour.
- Active devices that administer neither energy nor substances to the body nor are made for diagnosis.

Class I products cannot:

- Incorporate medicinal products (drugs) or animal tissue.
- Be intended for contraception or the prevention of sexually transmitted diseases.

for device characterization and testing. The exact nature of the test protocols is based on recommendations by USP, ISO, and others. It should be noted that Class I devices, if new, are also subject to the ISO guidelines. It should also be noted that, the FDA generally (but not strictly) now adheres to the ISO guidance on test requirements (see Tables 4.12 and 4.13).

Additional concerns with devices are considerations of their processing after production. For example, concerns have risen about the potential for allergies to develop to latex components and for male reproductive effects for diethylhexyl phthalate (DEHP) leaching from medical devices have led to the requirement that all such devices in either of these categories be appropriately labeled.

Devices that have systemic exposure need to be sterilized. Radiation and heat can be used for some devices, but others cannot be sterilized in these. Ethylene oxide or other chemical sterilants must be used, raising concerns that residual sterilants may present problems. At the same time, devices with exposure to the fluid path must be demonstrated to be neither pyrogenic nor hemolytic in their final manufactured form.

1. The selection of material(s) to be used in device manufacture and its toxicological evaluation should initially consider full characterization of the material, for example, formulation, known and suspected impurities, and processing.
2. The material(s) of manufacture, the final product, and possible leachable chemicals or degradation products should be considered for their relevance to the overall toxicological evaluation of the device.
3. Tests to be utilized in the toxicological evaluation should consider the bioavailability of the bioactive material, that is, nature, degree, frequency, duration, and conditions of exposure of the device to the body. This principle may lead to the categorization of devices, which would facilitate the selection of appropriate tests.
4. Any *in vitro* or *in vivo* experiments or tests must be conducted according to recognized good laboratory practices followed by evaluation by competent informed persons.
5. Full experimental data, complete to the extent that an independent conclusion could be made, should be available to the reviewing authority, if required.
6. Any change in chemical composition, manufacturing process, physical configuration, or intended use of the device must be evaluated with respect to possible changes in toxicological effects and the need for additional toxicity testing.
7. The toxicological evaluation performed in accordance with this guidance should be considered in conjunction with other information from other nonclinical tests, clinical studies, and post-market experiences for an overall safety assessment.

Device Categories: Definitions and Examples

The fundamental basis for evaluating device biocompatibility is based on the nature and cumulative duration of exposures of patients to the devices.

1. *Noncontact devices*: Devices that do not contact the patient's body directly or indirectly; examples include *in vitro* diagnostic devices.
2. *External devices*:
   a. *Intact surfaces*: Devices that contact intact external body surfaces only; examples include electrodes, external prostheses, and monitors of various types.
   b. *Breached or compromised surfaces*: Devices that contact breached or otherwise compromised external body surfaces; examples include ulcer, burn and granulation tissue dressings or healing devices, and occlusive patches.
3. *Externally communicating devices*:
   a. *Intact natural channels*: Devices communicating with intact natural channels; examples include contact lenses, urinary catheters, intravaginal and intraintestinal devices (sigmoidoscopes, colonoscopes, stomach tubes, gastroscopes), endotracheal tubes, and bronchoscopes.
   b. *Blood path, indirect*: Devices that contact the blood path at one point and serve as a conduit for fluid entry into the vascular system; examples include solution administration sets, extension sets, transfer sets, and blood administration sets.
   c. *Blood path, direct*: Devices that contact recirculating blood; examples include intravenous catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, and dialyzers, dialysis tubing, and accessories.
4. *Internal devices*:
   a. *Bone*: Devices principally contacting bone; examples include orthopedic pins, plates, replacement joints, bone prostheses, and cements.
   b. *Tissue and tissue fluid*: Devices principally contacting tissue and tissue fluid or mucus membranes where contact is prolonged; examples include pacemakers, drug supply devices, neuromuscular sensors and stimulators, replacement tendons, breast implants, cerebrospinal fluid drains, artificial larynx, vas deferens valves, ligation clips, tubal occlusion devices for female sterilization, and intrauterine devices.
   c. *Blood*: Devices principally contacting blood; examples include permanent pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts, blood monitors, internal drug delivery catheters, and ventricular assist pumps.

Biological Tests

Also required to properly utilize the tables in this chapter is a knowledge of the objectives of the specified biological tests. These can be considered as follows (Gad and Chengelis, 1998; Goering and Galloway, 1989):

Sensitization assay: Estimates the potential for sensitization of a test material and/or the extracts of a material using it in an animal and/or human. ISO (ISO, 1996 and 2008) and MHW procedures are contrasted in Table 4.2.

Irritation tests: Estimates the irritation potential of test materials and their extracts, using appropriate site or implant tissue such as skin and mucous membrane in an animal model and/or human. ISO and MHW procedures are contrasted in Table 4.3; and for eye irritation in Table 4.4.

TABLE 4.2
Contents of a Device Master File

1. EC declaration of conformity and classification according to Annex IX of the MDD
2. Name and address of the manufacturer's European responsible person
3. Product description, including:
   - All variants
   - Intended clinical use
   - Indications/contraindications
   - Operating instructions/instructions for use
   - Warnings/precautions
   - Photographs highlighting the product
   - Photographs highlighting the usage
   - Brochures, advertising, catalog sheets, marketing claims (if available)
   - Product specifications including:
     - Parts list, list of components
     - Specifications of materials used, including data sheets
     - List of standards applied
     - Details of substance(s) used (in the event of drug-device combination)
   - QA specifications (QC specs, in-process controls, etc.)
   - Labeling, accompanying documents, package inserts (DIN EN 289, prEN 980)
   - Instruction for use (prEN 1041)
   - Service manual
   - Product verification, including:
     - Testing data and reports, functionality studies, wet lab or benchtop testing
     - Materials certificates/reports on biological tests
     - EMC testing and certificates
     - Validation of the packaging/aging studies
     - Compatibility studies (connection to other devices)
   - Risk Analysis (DIN EN 1441)
   - Clinical Experience
4. List of requirements (Annex I) indicating cross-reference with documentation

Cytotoxicity: With the use of cell culture techniques, this test determines the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by test materials and/or extracts from the materials. ISO and MHW procedures are contrasted in Table 4.5.

Acute systemic toxicity: Estimates the harmful effects of either single or multiple exposures to test materials and/or extracts, in an animal model, during a period of less than 24 hours. ISO and MHW procedures are contrasted in Table 4.6.

Hematocompatibility: Evaluates any effects of blood contacting materials on hemolysis, thrombosis, plasma-proteins, enzymes, and the formed elements using an animal model. Traditionally, hemolysis has been the representative test employed to determine the degree of red blood cell lysis and the separation of hemoglobin caused by test materials and/or extracts from the materials in vitro. A broader range of primary tests (adding evaluations of thrombosis, coagulation, platelets, and immunology aspects) is currently recommended. ISO and MHW procedures for hemolysis are contrasted in Tables 4.7 and 4.8.

Implantation: Evaluates the local toxic effects on living tissue, at both the gross level and microscopic level, to a sample material that is surgically implanted into appropriate animal implant site or tissue, for example, muscle, bone; for 7–90 days. ISO and MHW procedures are contrasted in Tables 4.9 and 4.10.

TABLE 4.3
FDA Device Categories and Suggested Biological Testing (FDA, 2000)

Device Categories			Initial Evaluation								Supplemental Evaluation	
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)/pyrogenicity	Subchronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chromic toxicity	Carcinogenicity
Surface devices	Skin	A	•	•	•							
		B	•	•	•							
		C	•	•	•							
	Mucosal membrane	A	•	•	•							
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
	Breached compromised surface	A	•	•	•	0						
		B	•	•	•	0	0		0			
		C	•	•	•	0	•	•	0		0	
External communicating devices	Blood path indirect	A	•	•	•	•				•		
		B	•	•	•	•	0			•		
		C	•	•	0	•	•	•	0	•	•	•
	Tissue/bone dentin communicating	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		0	•
	Circulating blood	A	•	•	•	•		0		•		
		B	•	•	•	•	0	•	0	•		
		C	•	•	•	•	•	•	0	•	•	•
Implant devices	Bone/tissue	A	•	•	•	0						
		B	•	•	0	0	0	•	•			
		C	•	•	0	0	0	•	•		•	•
	Blood	A	•	•	•	•			•	•		
		B	•	•	•	•	0	•	•	•		
		C	•	•	•	•	•	•	•	•	•	•

A = Limited exposure (≤24 hours) B = Prolonged exposure (24 hours = 30 days) C = Permanent contact (>30 days)
• = FDA and ISO evaluation tests 0 = Additional tests for FDA

1. For these devices with possible leachables or degradation products, for example, absorbable surfaces, hemostatic agents, and so on, testing for pharmacokinetics may be required.
2. Reproductive and developmental toxicity tests may be required for certain materials used for specialized indications.
3. Considerations should be given to long-term biological tests where indicated in the table taking into account the nature and mobility of the ingredients in the materials used to fabricate the device.

Genotoxicity: The application of mammalian or non-mammalian cell culture techniques for the determination of gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by test materials and/or extracts from materials. Selected tests representing gene mutation tests (Ames or mouse lymphoma), chromosomal aberration tests (CHO) and DNA effects tests (mouse micronucleus and sister chromatid exchange) should generally be employed. ISO and MHW procedures are contrasted in Table 4.10.

Subchronic toxicity: The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of one day to less than 10% of the total life of the test animal (e.g., up to 90 days in rats).

TABLE 4.4
ISO Initial Evaluation Tests

Device Categories		Biological Tests								
Body contact duration **A—limited exposure** **B—prolonged or repeated exposure** **C—permanent contact**		**Cytotoxicity**	**Sensitization**	**Irritation or Intracutaneous**	**Acute systemic toxicity**	**Subchronic toxicity**	**Mutagenicity**	**Pyrogenicity**	**Implantation**	**Hemocompatability**
Surface devices										
Skin	A	x	x	x						
	B	x	x	x						
	C	x	x	x						
Mucous membranes	A	x	x	x						
	B	x	x	x						
	C	x	x	x		x	x			
Breached surface	A	x	x	x						
	B	x	x	x						
	C	x	x	x		x	x			
Externally communicating										
Blood path indirect	A	x	x	x				x		x
	B	x	x	x				x		x
	C	x	x		x	x	x	x		x
Tissue/bone communicating	A	x	x	x						
	B	x	x				x		x	
	C	x	x				x		x	
Internal devices										
Circulating blood	A	x	x	x	x			x		x
	B	x	x	x	x		x	x		x
	C	x	x	x	x	x	x	x		x
Implant devices										
Bone/tissue	A	x	x	x						
	B	x	x				x		x	
	C	x	x				x		x	
Blood	A	x	x	x	x			x	x	x
	B	x	x	x	x		x	x	x	x
	C	x	x	x	x	x	x	x	x	x

Chronic toxicity: The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of 10% to the total life of the test animal (e.g., over 90 days in rats).

Carcinogenesis bioassay: The determination of the tumorigenic potential of test materials and/or extracts from either single or multiple exposures, over a period of the total life (e.g., 2 years for rat, 18 months for mouse, or 7 years for dog).

Pharmacokinetics: To determine the metabolic processes of absorption, distribution, biotransformation, and elimination of toxic leachables and degradation products of test materials and/or extracts.

TABLE 4.5
ISO Special Evaluation Tests

Device Categories		Biological Tests			
Body contact duration **A—limited exposure** **B—prolonged or repeated exposure** **C—permanent contact (time limits to added)**		**Chronic toxicity**	**Carcinogenicity**	**Reproductive/ developmental**	**Degradation**
Surface devices					
Skin	A				
	B				
	C				
Mucous membranes	A				
	B				
	C				
Breached surface	A				
	B				
	C				
Externally communicating					
Blood path indirect	A				
	B				
	C	x	x		
Tissue/bone communicating	A				
	B				
	C		x		
Internal devices					
Circulating blood	A				
	B				
	C	x	x		
Bone/tissue	A				
	B				
	C	x	x		
Blood	A				
	B				
	C	x	x		

Reproductive and developmental toxicity: The evaluation of the potential effects of test materials and/or extracts on fertility, reproductive function, and prenatal and early postnatal development.

The tests for leachables such as contaminants, additives, monomers, and degradation products must be conducted by choosing appropriate solvent systems that will yield a maximal extraction of leachable materials to conduct biocompatibility testing. See Gad and Gad-McDonald (2015) for more information on the issues behind sampling, sample preparation, and solvents.

The effects of sterilization on device materials and potential leachables, as well as toxic by-products, as a consequence of sterilization should be considered. Therefore, testing should be performed on the final sterilized product or representative samples of the final sterilized product. Table 4.10 presents the basis for test selection under the Tripartite Agreement.

TABLE 4.6
Japanese MHLW Test Selection Guidelines

Device Categories		Initial Evaluation						Supplemental Evaluation					
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity	Genotoxicity	Pyrogen	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Surface Devices	Skin	A	X	X	X								
		B	X	X	X								
	Mucosal membrane	C	X	X	X								
		A	X	X	X								
		B	X	X	X								
		C	X	X	X		X	X					
	Breached/compromised surface	A	X	X	X								
		B	X	X	X								
		C	X	X	X		X	X					
External Communicating Devices	Blood path indirect	A	X	X	X	X			X		X		
		B	X	X	X	X			X		X		
		C	X	X		X	X	X	X		X	X	X
	Tissue/bone dentin communicating	A	X	X	X								
		B	X	X				X		X			
		C	X	X				X		X			X
	Circulating blood	A	X	X	X	X			X		X		
		B	X	X	X	X		X	X		X		
		C	X	X	X	X	X	X	X		X	X	X
Implant Devices	Bone/tissue	A	X	X	X								
		B	X	X				X		X			
		C	X	X				X		X		X	X
	Blood	A	X	X	X	X			X	X	X		
		B	X	X	X	X		X	X	X	X		
		C	X	X	X	X	X	X	X	X	X	X	X

A = Temporary contact (<24 hours), B = Short- and medium-term contact (24 hours – 29 days), and C = Long-term contact (>30 days).

TABLE 4.7
Differences between Sensitization Test Procedures Required by ISO 10993-10 and the MHLW Guidelines

ISO 10993-10	MHLW 1995
Sample Preparation:	
Extraction in polar and/or nonpolar solvents.	Two extraction solvents, methanol and acetone, recommended.
Extraction ratio:	
Extraction ratio is dependent on thickness of device or representative portion.	Specific extraction ratios: 10:1 (volume solvent: weight sample).
Extract used for testing. If extraction is not possible, the adjuvant and patch test can be utilized.	Residue obtained from extraction is redissolved and used for testing. (If residue does not dissolve in DMSO, or a sufficient amount of residue is not obtained, the adjuvant and patch test is recommended). Sufficient amount of residue: 0.1%–0.5% (weight residue: weight test material).

TABLE 4.8
Differences in Intracutaneous Reactivity Test Procedures Required by ISO 10993-10 and the MHLW Guidelines

ISO 10993-10	MHLW
Number of test animals:	
Three rabbits for 1 to 2 extracts	Two rabbits for each extract
Number of test/control injections per extract:	
Five tests and five control injections	10 tests and 5 control injections
Evaluation of responses:	
Quantitative comparison of responses of test and control responses	Qualitative comparison of test and control responses

TABLE 4.9
Differences in Eye Irritation Testing Procedures Outlined in ISO 10993-10 and the MHLW Guidelines

ISO 10993-10	MHLW 1995
Time of exposure:	
1 second	30 seconds
Grading scale:	
Classification system for grading ocular lesions	Draize or McDonald-Shadduck scale

United States Pharmacopoeial Testing

The earliest guidance on what testing was to be done on medical devices was provided in the USP and other pharmacopoeias. Each of the major national pharmacopoeias offers somewhat different guidance. The test selection system for the USP (presented in Table 4.10), which classified plastics as Classes I through VI, is now obsolete and replaced in usage by the other guidelines presented here. But the actual descriptions of test types, as provided in the USP (and presented in the appropriate chapters later in this book) are still very much operative (USP, 1994).

TABLE 4.10
Differences Between Cytotoxicity Test Procedures Specified by ISO 10993-5 and the MHLW Guidelines (MHLW 1995)

ISO 10993-10	MHLW 1995
Number of cells per dish:	
0.5–1 million cells	40 to 200 cells per dish
Extraction ratio:	
60 cm^2 per 20 ml if thickness 80.5 mm 120 cm^2 per 20 ml if thickness 70.5 mm or 4 g per 20 ml	5 cm^2/ml or 1 g/10 ml
Exposure period:	
Typically, 24–72 hours (2 hours for filter diffusion test)	6–7 days
Toxicity determination:	
Visual grading and/or quantitative assessments	Quantification of surviving colonies
Positive controls:	
Materials providing a reproducible cytotoxic response (e.g., organo-tin-impregnated polyvinyl chloride)	Segmented polyurethane films containing 0.1% zinc diethyldithiocarbamate and 0.25% zinc dibutyldithiocarbamate

There are British, European, and Japanese pharmacopoeias, of which the latter requires the most attention due to some special requirements still being operative if product approval is desired.

ISO Testing Requirements

The European Economic Community (EEC) adopted a set of testing guidelines for medical devices under the aegis of ISO (ISO, 2008; The Gray Sheet, 1992). The ISO 10993 guidelines for testing provide a unified basis for international medical device biocompatibility evaluation, both in terms of test selection (as presented in Tables 4.11 and 4.12) and test design and interpretation (Table 4.13). In 1996, the FDA also announced that it would adhere to ISO 10993 standards for device biocompatibility evaluation and in 2016 promulgated an updated adaptation of this guidance (FDA, 2016).

This international standard specifies biological testing methods of medical and dental materials and devices and their evaluation regarding their biocompatibility. Because of the many materials and devices used in these areas, the standard offers a guide for biological testing.

Ministry of Health and Welfare Requirements

The Japanese ISO test selection guidelines vary from those of FDA and ISO and are summarized in Tables 4.14 and 4.15 (MHLW, 2012). In the matter of sample preparation, US FDA currently accepts sensitization and intracutaneous reactivity testing done for submission in Japan, though the extraction conditions are less strenuous than those for FDA.

Actual test performance standards also vary, as shown in Tables 4.3–4.10.

Committees dealing with materials and devices must decide on tests and test series relevant to the respective materials and devices. It is the responsibility of the product committees to select adequate test methods for products. The standard contains animal tests but tries to reduce those tests to the justifiable minimum. Relevant international and national regulations must be observed when animals are used.

ISO 10993 is based on existing national and international specifications, regulations, and standards wherever possible. It is open to regular review whenever new research work is presented to improve the state of scientific knowledge. Tables 4.3 and 4.4 provide the test matrices under ISO 10993. Subsequently, specific guidance on individual test designs, conduct, and interpretation has been provided as subparts 2–11 of ISO-10993 (Table 4.13) (AAMI, 2006).

TABLE 4.11
Comparison of Grading Scales Used to Score Responses of Test Animals to ASTM and ISO/USP Procedures

	ASTM	ISO/USP
Response	**Description**	
Normal, no symptoms	Mouse exhibits no adverse physical symptoms after injection.	
Slight	Mouse exhibits slight but noticeable symptoms of hypokinesis, dyspnea, or abdominal irritation after injection.	
Moderate	Mouse exhibits definite evidence of abdominal irritation, dyspnea, hypokinesis, ptosis, or diarrhea after injection. (Weight usually drops to between 15 g and 17 g.)	
Marked	Mouse exhibits prostration, cyanosis, tremors, or severe symptoms of abdominal irritation, diarrhea, ptosis, or dyspnea after injection. (Extreme weight loss; weight usually less than 15 g.)	
Dead, expired	Mouse dies after injection.	
	Interpretation	***Interpretation***
	The test is considered negative if none of the animals injected with the test article extracts shows a significantly greater biological reaction than the animals treated with the control article.	The test is considered negative if none of the animals injected with the test article shows a significantly greater biological reaction than the animals treated with the control article.
	If two or more mice show either marked signs of toxicity or die, the test article does not meet the requirements of the test.	If two or more mice die or show signs of toxicity, such as convulsions or prostration, or if three or more mice lose more than 2 g of body weight, the test article does not meet the requirements of the test.
	If any animals treated with a test article shows slight signs of toxicity, and not more than one animal shows marked signs of toxicity or dies, a repeat test using freshly prepared extract should be conducted using groups of 10 mice each. A substantial decrease in body weight for all animals in the group, even without other symptoms of toxicity, requires a retest using groups of 10 mice each. In the repeat test, the requirements are met if none of the animals injected with the test article shows a substantially greater reaction than that observed in the animals treated with the control article.	If any animal treated with a test article shows only slight signs of biological reaction, and not more than one animal shows gross signs of biological reaction or dies, a repeat test should be conducted using groups of 10 mice. On the repeat test, all 10 animals must not show a significantly greater biological reaction than the animals treated with the control article.

CE Marking of Devices

After June 14, 1998, all medical products distributed in Europe have had to bear the Conformité Européene (CE) mark. ISO 9000 certification supplements and supports an assessment of conformity to the Medical Devices Directive (MDD), which must be performed by a certification body appointed by the EU member states (Haindl, 1997). To qualify for the CE mark, manufacturers of Class IIa, IIb, and III devices must be certified by a notified body (a private organization, which is recognized by the national health authorities) to Annex II, V, or VI of the MDD (also known as 93/42/EEC) and comply with the essential requirements of the directive. Meeting these requirements is less difficult than meeting those for the current (June 2016) FDA expectation. However, devices, once approved for market by FDA, are subsequently

TABLE 4.12
Differences in Hemolysis Test Procedures Recommended by ISO 10993-4 and the MHLW Guidelines

ISO 10993-4	MHLW 1995
Hemolysis can be assessed by any of several validated methods to assay hemoglobin in plasma.	Hemolytic index is assessed by measuring hemoglobin at 1, 2, and 4 hours by spectrophotometric methods. The hemolysis over this period is expressed as a percentage of the positive control.

TABLE 4.13
Comparison of Pyrogen Test Procedures Required by ISO 10993-11 and the MHLW Guidelines

ISO 10993-11	MHLW 1995
Number of animals:	
Three rabbits required; comparison of febrile response in test animals to baseline temperature for evaluation of pyrogenicity potential	Three rabbits (test) required; comparison to baseline temperature is evaluated as index of pyrogenicity potential
Test duration:	
Test measurement intervals: every 30 minutes for 3 hours	Test measurement intervals: every hour for 3 hours
Evaluation:	
Cutoff for positive febrile response: 0.5°C	Cutoff for positive febrile response: 0.6°C

TABLE 4.14
Differences in ISO 10993-3 and the MHLW Guidelines for Assessing the Effects of Device or Material Implantation

ISO 10993-3	MHLW 1995
Time point(s) of assessment:	
Sufficient to achieve steady state (e.g., 2, 4, 6, and 12 weeks)	7 days and 4 weeks
Number of animals:	
At least three per time period of assessment	At least four per time period
Number of samples of evaluation:	
At least eight per time period for test and control	No minimum number specified
Evaluation criteria:	
Comparative evaluation of responses to test and control materials	If more than two of the four test sites in each animal exhibit a significant response compared to control sites, the test is considered positive

grandfathered against subsequently having to meet updated biocompatibility testing requirements. This is not the case for a CE mark. The notified bodies are required to perform periodic audits of all approved devices, and if test guidelines have been made, more strenuous audit lead to requirements to repeat previously passed testing to be in accordance with revised testing guidelines. Manufacturers of active implantables and IVDs have separate directives to contend with. When auditing for compliance, the notified body will check a number of items in addition to a manufacturer's quality assurance (QA) system, including technical files, sterility assurance measures, subcontracting procedures, recall and vigilance systems, and

TABLE 4.15
Differences in Genotoxicity Testing Procedures Required by ISO 10993-3 and the MHLW Guidelines

ISO 10993-10	MHLW 1995
Extraction vehicles:	
A physiological medium is used and, where appropriate, a solvent (e.g., dimethyl sulfoxide).	Recommends methanol and acetone as extracting vehicles.
Extraction:	
Extract test material and test the extract or dissolve material in solvent and conduct test. The conditions of extraction should maximize the amount of extractable substances, as well as subject the test device or material to the extreme conditions it may be exposed to, without causing significant degradation. Extraction ratio is dependent on thickness of test material.	Extract at room temperature at a ratio of 10:1 (solvent: material) and obtain residue (at least 0.1%–0.5% [weight of residue/weight of test material]), redissolve in appropriate solvent and test residue. If sufficient residue is unobtainable, extract test material (in ethanol, acetone, or DMSO at 10 g of test material per 20 ml for the Arnes mutagenicity assay, and in cell culture medium at 120 cm^3 or 4 g/20 ml for the chromosomal aberration assay), at 37°C for 48 hours and test extract. The Ames mutagenicity assay is conducted with a volume of 200 µl per plate.

declarations of conformity. Depending on the classification and certification route, some devices will also require an (European Community) EC-type examination or a design review by the notified body.

Class I product manufacturers, who require minimal interaction with a notified body, appear to be the clear winners in this scheme, but even they must deal with several vague or confusing requirements (see Table 4.15). Simply classifying their products according to the dictates of 93/42/EEC, Annex IX, can be a tricky affair, and faulty classification can lead to bigger problems. The simplified flowcharts in Figure 4.2 should help manufacturers determine whether their products qualify as Class I devices. For more difficult products, manufacturers may need to hire a consultant or obtain a suitable software program.

Classification is based on the intended and declared use of a product, not solely on its salient features. The Class I designation usually—but not always—excludes sterile products and measuring devices that measure physiological parameters or require a high degree of accuracy. So, for example, a reusable scalpel is Class I, but a sterile scalpel is Class IIa; a scalpel blade for the reusable device is Class I, but if it is supplied sterile, it is Class IIa; a scalpel blade for the reusable device is Class I but if it is supplied sterile, it is Class IIa. A stethoscope, a simple graduated syringe (not for injection pumps), and a measuring spoon for administering an expectorant are not considered measuring devices, although a hand-driven blood-pressure gage and a digital thermometer are.

All of the classification rules are included in the directive, but they're not easy to understand. An EC working group has drawn up a separate paper known as *MEDDEV 10/93* to explain the rules and provide some practical guidelines (EC, 1996). For example, the directive stipulates that reusable surgical instruments belong in the Class I designation if they are not intended to be used for more than an hour of continuous use. According to this definition, items such as scissors and tweezers, even if they are used in a six-hour operation, are still considered Class I devices because they are not used continuously during that time.

Even if a Class I product is supplied sterile, the manufacturer must issue a self-declaration of conformity. In this case, the manufacturer need only certify the quality control (QC) system governing those aspects of manufacture concerned with securing and maintaining sterile conditions. If the device is packaged and sterilized by a company that works with a certified process, then the manufacturer must only validate the process for the particular device and submit the results to a notified body. The manufacturer still needs certification by a notified body regarding the performance aspects

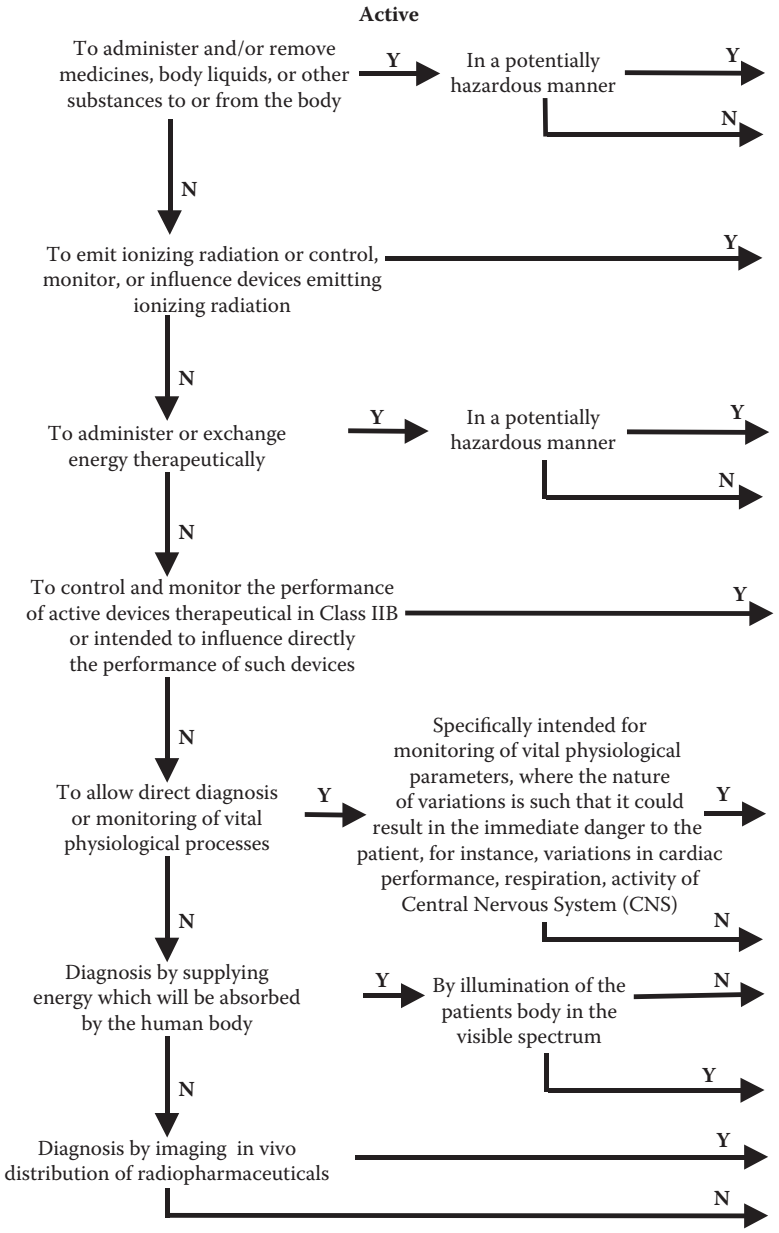

FIGURE 4.2 Flowchart for classification of active device. (Adapted from Bunger, M. and Tummler, H.P., *Med. Dev. Technol.*, 5, 33–39, 1994. With permission.)

relating to sterility and measurement function; the notified body will also want to inspect the manufacturer's facility. Nonetheless, the procedure is far less complicated than a full production audit.

All manufacturers applying for CE marking privileges—including manufacturers of Class I devices—must prepare the proper technical documentation; appoint a *responsible person* within the EEC; design product labels and labeling according to 93/42/EEC, Annex I, paragraph 13; and sign a declaration of conformity. The technical dossier should not pose a major problem for manufacturers familiar with device master files. A list of required dossier contents is given in Table 4.16. For biological material testing, Europe uses the ISO 10993 (EN 30993) protocols, but also accepts test results according to the Tripartite agreement (or USP XXIII). Every electrical device must also be proven to comply

TABLE 4.16
Classification of Plastics (USP XXIII)

Plastic Classes[a]						Tests to Be Conducted			
I	II	III	IV	V	VI	Test Material	Animal	Dose	Procedures[b]
x	x	x	x	x	x	Extract of sample in sodium chloride inspection	Mouse	50 ml/kg	A (iv)
x	x	x	x	x	x		Rabbit	0.2 ml/animal at each of 10 sites	B
x	x	x	x	x		Extract of sample in 1 in 20	Mouse	50 ml/kg	A (iv)
x	x	x	x	x		Solution of alcohol in sodium chloride injection	Rabbit	0.2 ml/animal at each of 10 sites	
	x		x	x		Extract of sample in polyethylene glycol 400	Mouse	10 g/kg	A (ip)
		x	x				Rabbit	0.2 ml/animal at each of 10 sites	
		x	x	x	x	Extract of sample in vegetable oil	Mouse	50 ml/kg	A (ip)
			x	x	x		Rabbit	0.2 ml/animal at each of 10 sites	B
		x			x	Implant strips of sample	Rabbit	4 strips/animal	C

[a] Tests required for each class are indicated by "x" in appropriate rows.

[b] Legend: A (ip), Systemic injection test (intraperitoneal); A (iv), Systemic injection test (intravenous); B, Intracutaneous (Intracutaneous); C, Implantation test (intramuscular implantation).

The table lists the biological tests that might be applied in evaluating the safety of medical devices and/or polymers. This does not imply that all the tests listed under each category will be necessary or relevant in all cases. Tests for devices made of metals, ceramics, biological materials, and so on, are not included here but are under consideration.

Categorization of medical devices is based on body contact and contact duration.

with the Electromagnetic Compatibility (EMC) requirements defined in the MDD; suppliers of preassembled electrical components may have the appropriate test results already available. Reformatting an existing device master file is not necessary, only creating an index that cross-references the essential requirements of the directives with the device file contents. The master file is a controlled document, as defined in ISO 9000, and manufacturers would do well to regard it as highly confidential.

The technical dossier is closely linked to the responsible person, a representative in the EEC governed by European law and authorized by the manufacturer to oversee routine regulatory affairs. Specifically, the responsible person must ensure compliance with the European vigilance system, which covers both post-market surveillance and adverse-incident reporting. For example, if a patient were injured by a device, or if a patient would have been injured had the caregiver not intervened, the responsible person would have to investigate the incident together with the device's manufacturer and file a report with the competent authorities. Moreover, the European authorities must be able to obtain the master file in case of trouble; therefore, the manufacturer must either store the file or its abbreviated form with the responsible person or draw up a contractual agreement that gives

the agent the right to access the master file without delay if required by the authorities. The agent must be available all year, as the time frame for notification could be as short as 10 days. Ideally, the responsible person should be familiar with the national regulation in all member states.

The simplest way to maintain a European address will be to appoint a distributor as their responsible person, although this course is not without potential problems. The selected distributor does not need certification as long as the manufacturer's name and CE mark are on the product labeling. The name of the responsible person must also appear on the label, package insert, or outer packaging, even if the product is sold by a completely different distributor in another country. There is no official rule or proposal regarding how many responsible persons a manufacturer should have, but each one must appear on the labeling; therefore, appointing more than one is of limited use. The responsible person should be selected with great care; device master files (Tables 4.16 and 4.17) must be made available to the responsible person in the event of patient injury or near injury, and many distributors are potential competitors. Class I devices, by nature, will rarely lead to patient injury, but manufacturers should still consider labeling issues when choosing a representative. It's easy to change distributors, but changing the responsible person means changing all the product labeling. As an alternative, manufacturers can contract with a professional agency to serve as a representative completely independent from any distribution network.

The issue of labeling is itself a source of contention. Not all countries have decided yet whether they will insist on having their own language on device labels. Many countries have rather imprecise

TABLE 4.17
ANSI/AAMI/ISO Standards

	ISO Designations	Most Recent Revision
Evaluation and testing	10993-1	2009
Animal welfare requirements	10993-2	2006
Tests for genotoxicity, carcinogenicity and reproductive toxicity	10993-3	2014
Selection of tests for interactions with blood	10993-4	2017
Tests for *in vitro* cytotoxicity	10993-5	2009
Tests for local effects after implantation	10993-6	2016
Tests for irritation and delayed-type hypersensitivity	BE78	2002
Ethylene oxide sterilization residuals	10993-7	2008
CANCELLED	10993-8	—
Framework for identification and quantification of potential degradation products	10993-9	2014
Tests for Irritation and Skin Sensitization	10993-10	2014
Tests for systemic toxicity	10993-11	2006
Sample preparation and reference materials	10993-12	2012
Identification and quantification of degradation products from polymeric devices	10993-13	2010
Identification and quantification of degradation products from ceramics	10993-14	2001
Identification and quantification of degradation products from metals and alloys	10993-15	2000
Toxicokinetic study design for degradation products and leachables from medical devices	10993-16	2014
Establishment of allowable limits for leachable substances	10993-17	2008
Chemical characterization of Materials	10993-18	2006
Physio-chemical, morphological, and topographical characterization of materials	10993-19	2006
Chemical characterization of materials	BE83	2006
Principles and methods for immunotoxicology testing of medical devices	10993-20	2006
Guidance of NanoMaterials	10993-22	2017
Guidance on test to evaluate genotoxicity—Suplement to ISO 10993-3	10993-33	2015
Clinical Investigation of medical devices for human subjects—Good Clinical Practice	14155	2011

rules dictating that their national language must appear only if necessary. Manufacturers can reduce potential trouble by using the pictograms and symbols defined in the harmonized European standard EN 980. For instructions of use, manufacturers are advised to print all 12 languages spoken in the European Economic Area. The requirements for labeling are presented in Annex I, paragraph 13, of the MDD; some devices may be subject to additional requirements outlined in product standards.

Class I products fall under the jurisdiction of local authorities, but who serves as those authorities may differ from country to country. In Germany, for example, there are no clear-cut regulations that define the reach of the local authorities, except in the case of danger to the patient. European product liability laws (more or less) give the consumer the right to sue anybody in the trade chain. Normally, claims would be filed against the manufacturer, but it is possible that there will be claims against a responsible person. This is a rather new legal situation, and the rules will be determined by court decisions. It is hoped that Class I products will not instigate many court actions, but clearly, even manufacturers of Class I devices will have a host of new concerns under the CE marking scheme.

Risk Assessment

The reality is that not all materials used on devices are entirely safe. Generally, if one looks long enough at small enough quantities, some type of risk can be associated with every material. Risk can be defined as the possibility of harm or loss. Health risk, of course, is the possibility of an adverse effect on one's health. Risk is sometimes quantified by multiplying the severity of an event times the probability the event will occur, so that

$$\text{Risk} = \text{Severity} \times \text{Probability}$$

While this equation appears useful in theory, in practice it is difficult to apply to the biological safety of medical devices. The process known as health-based risk assessment attempts to provide an alternative strategy for placing health risks in perspective (Stark, 1998; AAMI, 1998).

Standards and Guidances

A paradigm for the risk assessment process has been detailed in a publication prepared by the US National Academy of Sciences (Hayes, 2014). Although devised primarily for cancer risk assessment, many of the provisions also apply to the assessment of other health effects. The major components of the paradigm are (1) hazard identification, (2) dosage-response assessment, (3) exposure assessment, and (4) risk characterization (Ecobichon, 1992).

The general approach to risk assessment was adapted to medical devices via the draft CEN standard *Risk Analysis*, published in 1993,[1] and via the ISO standard, *ISO 14538—Method for the establishment of Allowable Limits for Residues in Medical Devices Using Health-Based Risk Assessment* (ISO, 2008) and ISO 14971 - "Medical devices -- Application of risk management to medical devices" (ISO, 2007).[2]

The FDA is also working to develop a health-based risk assessment protocol adapted to medical devices. Informally called the Medical Device Paradigm, the document is not yet generally available (Brown and Stratmeyer, 1997).[3]

Some manufacturers may object to the fact that regulators are once again attempting to impose a *drug model* on medical devices. However, we shall see in the following pages that the judicious application of these risk assessment principles can provide a justification for using materials that carry with them some element of risk, and that may, under traditional biocompatibility testing regimes, be difficult to evaluate or be deemed unsuitable for medical device applications.

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[1] *CEN BTS 3/WG 1—Risk Analysis* is available through the British Standards Institute.

[2] Available from the Association for the Advancement of Medical Instrumentation, 3330 Washington Blvd., Ste. 400, Arlington, VA 22201.

[3] Draft copies of the Medical Device Paradigm may be obtained by contacting Dr. Melvin Stratmeyer, FDA Center for Devices and Radiological Health, HFZ-112, Division of Life Sciences, Office of Science and Technology, FDA, Rockville, MD 20857.

Method

Hazard identification: The first step in the risk assessment process is to identify the possible hazards that may be presented by a material. This is accomplished by determining whether a compound, an extract of the material, or the material itself produces adverse effects, and by identifying the nature of those effects. Adverse effects are identified either through a review of the literature or through actual biological safety testing.

Dose-response assessment: The second step is to determine the dose response of the material—that is, what is the highest weight or concentration of the material that will not cause an effect? This upper limit is called the *allowable limit*. There are numerous sources in the literature of data from which to determine allowable limits; some will be more applicable than others, and some may require correction factors.

Exposure assessment: The third step is to determine the exposure assessment by quantifying the *available dose* of the chemical residues that will be received by the patient. This is readily done by estimating the number of devices to which a patient is likely to be exposed in a sequential period of use (for instance, during a hospital stay) or over a lifetime. For example, a patient might be exposed to 100 skin staples following a surgical procedure, or to two heart valves in a lifetime; thus, the amount of residue available on 100 skin staples or two heart valves would be determined.

Risk characterization: Characterizing the risk constitutes the final step of the process. The allowable limit is compared with the estimated exposure: if the allowable limit is greater than the estimated exposure by a comfortable safety margin, the likelihood of an adverse event occurring in an exposed population is small, and the material may be used.

Case Studies

We can best get a sense of how these standards work by looking at some actual medical case studies that illustrate the risk assessment process (Stark, 1997).

Nitinol implant: Nitinol is an unusual alloy of nickel and titanium that features the useful property of *shape memory*. A nitinol part can be given a particular shape at a high temperature, then cooled to a low temperature and compressed into some other shape; the compressed part will subsequently deploy to its original shape at a predetermined transition temperature. This feature is particularly beneficial for vascular implant applications in which the shape of the device in its compressed state eases the insertion process. The nitinol deploys as it is warmed by the surrounding tissue., expanding to take on the desired shape of a stent, filter, or other device. The transition temperature depends on the alloy's relative concentrations of nickel and titanium: a typical nickel concentration of 55%–60% is used in medical devices, since this gives a transition temperature at approximately the temperature of the body (37°C).

Hazard identification: One concern with using nitinol in implant applications is the potential release of nickel into the body. Although nickel is a dietary requirement, it is also highly toxic—known to cause dermatitis, cancer, after inhalation, and acute pneumonitis from inhalation of nickel carbonyl, and to exert a toxic effect on cellular reproduction. It is a known sensitizer, with approximately 5% of the domestic population allergic to this common metal, probably through exposure from costume jewelry and clothing snaps. *The biocompatibility question at hand is whether or not* in vivo *corrosion of nitinol releases unsafe levels of nickel.*

Dose-response assessment: A search of the world medical literature revealed that the recommended safe level of exposure to nickel in intravenous fluids is a maximum of

35 µg/day (Stark, 1997). This value can be taken as an allowable limit of nickel exposure for a 70-kg (154-lb) adult.

The intravenous fluid data are based on subjects that are comparable to the patients who will be receiving nitinol implants. The data are for humans (not animals), for ill patients (not healthy workers or volunteers), and for similar routes of exposure (intravenous fluid and tissue contact). For these reasons, no safety correction factor need to be applied to the allowable limit of exposure.

Exposure assessment: The available dose of nickel from nitinol implants can be estimated from data found in the literature. In one study, dental arch wires of nitinol were extracted in artificial saliva, and the concentration of nickel measured in the supernatant. Corrosion reached a peak at day 7, then declined steadily thereafter. The average rate of corrosion under these conditions was 12.8 µg/day/cm^2 over the first 28 days.

Risk characterization: A comparison of the available dose with the allowable limit for intravenous fluid levels shows that there is approximately a threefold safety margin, assuming that the implanted device is a full 1 cm^2 in surface area. (Devices with less surface area will contribute even less to the nickel concentration and have an even larger safety margin.) Considering the high quality of the data, a threefold safety margin is sufficient to justify using nitinol in vascular implants.

Wound-dressings: Today's wound dressings are highly engineered products, designed to maintain the moisture content and osmatic balance of the wound bed so as to promote optimum conditions for wound healing. Complex constructions of hydrocolloids and superabsorbers, these dressings are sometimes used in direct tissue contact over full-thickness wounds that penetrate the skin layers.

Hazard identification: There have been reports in the literature of patients succumbing to cardiac arrest from potassium overload, with the wound dressing as one of the important contributors of excess potassium in the bloodstream. The effects of potassium on cardiac function are well characterized. Normal serum levels for potassium are 3.8 to 4 milliequivalents per liter (mEq/L). As the potassium concentration rises to 5–7 mEq/L, a patient can undergo cardiac arrest and die. *The biocompatibility issue to be explored is whether or not a wound-dressing formulation might release dangerous levels of potassium if used on full-thickness wounds.*

Dose-response assessment: An increase of approximately 1 mEq/L of potassium is unlikely to provoke mild adverse events in most patients. Assuming the average person's blood volume is 5 L, a one-time dose of 5 mEq of potassium may begin to cause adverse reactions. This value can be considered to be the allowable limit of potassium for most patients.

Exposure assessment: Let us suppose that each dressing contains 2.5 g of potassium bicarbonate. Since the molecular weight of potassium bicarbonate is 100 g/mole, each dressing contains 0.025 mole of sodium bicarbonate, or 0.025 mEq of potassium ion. If a patient were to use four dressings in a day, the available dose of potassium would be 0.1 mEq/day.

Risk characterization: Comparing the available dose of potassium (0.1 mEq) to the allowable limit (5 mEq) shows that there is a 50-fold safety margin. Considering that patients may be small in size, may have kidney impairment, or may receive potassium from additional sources, such as intravenous fluids, this safety margin is too narrow, and so the dressing should be reformulated.

Perchloroethylene solvent: A manufacturer of metal fabricated parts uses perchloroethylene to clean the finished pieces. Perchloroethylene has many advantages as a cleaner and degreaser: it is highly volatile, does not damage the ozone layer, and is very effective as a precision cleaning solvent. The most common use of perchloroethylene is in the dry-cleaning industry, but it is also commonly used in the electronics industry to clean circuit boards.

Hazard identification: The downside of perchloroethylene is that is it highly toxic, with a material safety data sheet several pages in length listing adverse effects ranging from dizziness to death. Biocompatibility testing on solvent-cleaned parts would be meaningless; the solvent concentration on the part is so small that any effects of the solvent would be masked by the natural biological process of the test animals. *The biocompatibility question that must be answered is whether or not sufficient residual perchloroethylene remains on the cleaned metal parts to pose a health hazard.*

Dose-response assessment: Threshold Limit Values (TLVs) are values that indicate the maximum level of a chemical that a healthy worker could take in daily over the course of his or her work life without experiencing any adverse effects (ACGIH, 1986; AHHA, 1980). The TLV for perchloroethylene is 50 ppm/day (50 ml of perchloroethylene per 10^3 L of air) by inhalation. The average person inhales 12,960 L of air per day, making this equivalent to 650 ml of perchloroethylene per day. Since the vapor density of perchloroethylene is 5.76 g/L, the TLV is equal to 3.7 g of perchloroethylene per day by inhalation.

Because TLVs for inhalation—as opposed to direct tissue exposure—are determined based on healthy individuals (not ill patients), we will divide the TLV by an uncertainly factor of 100, that is, 10 to account for a different route of exposure and 10 to account for healthy-to-ill persons. By this method, we obtain an allowable perchloroethylene limit of 37 mg/day.

Exposure assessment: To calculate an available dose of perchloroethylene, we need some additional information. In this case, the manufacturer brought a number of cleaned metal pieces into equilibrium within a closed jar, then analyzed the headspace above the pieces by using a high-pressure liquid chromatography to determine the concentration of perchloroethylene released. The concentration of perchloroethylene was undetectable by high-performance liquid chromatography. Since the limits of this analytical method are 2 ppb, this value was taken as the concentration of perchloroethylene in the headspace. Taking the weight of the metal pieces, the number of pieces tested, and the volume of the headspace, it was calculated that the amount of perchloroethylene per single piece was a maximum of 1.0 ng/piece (nanogram/piece). If we suppose that a patient might be exposed to a maximum of 50 pieces over a lifetime, then the maximum available dose of perchloroethylene from the pieces would be 50 ng.

Risk characterization: A comparison of the available dose (50 ng) to the allowable limit (37 mg/day) indicates an ample safety margin.

Ligature material: A manufacturer purchases commercial black fishing line to use as a ligature in a circumcision kit. Because the ligature is not *medical grade*, a cytotoxicity test is routinely conducted as an incoming inspection test. It was assumed that a negative cytotoxicity test would be associated with an acceptable incidence of skin irritation.

Hazard identification: A newly received lot of the fishing line failed the cytotoxicity test. The extraction ration of this material—of indeterminate surface area—was 0.2 g/ml, with a 0.1-ml aliquot of sample extract being applied to a culture dish. Thus, 0.2 g/ml × 0.1 ml = 0.02 g represents a toxic dose of fishing line.

Dose-response assessment: A titration curve was obtained on the sample extract. If the sample was diluted 1:2, the test was still positive; however, if the sample was diluted 1:4, the test was negative. Thus, 0.02 g/4 = 0.005 g of fishing line, the maximum dose that is not cytotoxic. This value was called the allowable limit of fishing line.

Exposure assessment: Each circumcision kit contained about 12 inches of line, but only about 4 inches of material was ever in contact with the patient. Since an 8-yd line was determined to weigh 5 g, the available dose of fishing line was calculated to be 5 g/288 in. × 4 in. = 0.07 g.

Risk characterization: A comparison of the available dose (0.07 g) with the allowable limit (0.005 g) convinced the manufacturer to reject the lot of fishing line.

Sources of Data

Data for calculating the allowable limit of exposure to a material can come from many sources, most of them promulgated by industrial and environmental hygienists and related agencies (Hayes, 2014).

TLVs are time-weighted average concentrations of airborne substances. They are designed as guides to protect the health and well-being of workers repeatedly exposed to a substance during their entire working lifetime (7–8 hr/day, 40 hr/wk). TLVs are published annually by the American Conference of Governmental Industrial Hygienists (ACGIH, 1986). Biological Exposure Indices (BEIs) are also published annually by ACGIH. These are the maximum acceptable concentrations of a substance at which a worker's health and well-being will not be compromised.

Other published guides include Workplace Environmental Exposure Levels (WEELs), from the American Industrial Hygiene Association (AIHA) (1980); Recommended Exposure Limits (RELs), from the US National Institute for Occupational Safety and Health; and Permissible Exposure Limits (PELs), from the US Occupational Safety and Health Administration. In the United States, PELs have the force of law.

Another important limit measurement, Short-Term Exposure Limits (STELs), are defined as the maximum concentration of a substance to which workers can be exposed for a period of up to 15 minutes continuously, provided that no more than four excursions per day are permitted, and with at least 60 minutes between exposure periods. The STEL allows for short-term exposures during which workers will not suffer from irritation, chronic or irreversible tissue damage, or narcosis of sufficient degree to increase the likelihood of injury, impair self-rescue, or materially reduce work efficiency. Some substances are given a *ceiling*—an airborne concentration that should not be exceeded even momentarily. Examples of substances having ceilings are certain irritants whose short-term effects are so undesirable that they override consideration of long-term hazards.

Uncertainty Factors

An uncertainty factor is a correction that is made to the value used to calculate an allowable limit. It is based on the uncertainty that exists in the applicability of the data to actual exposure conditions. Typically, uncertainty factors range in value from 1 to 10. For example, a correction factor of 10 might be applied for data obtained in animals rather than humans, or to allow for a different route of exposure. In other words, for every property of available data that is different from the actual application, a correction factor of between 1 and 10 is applied. If our first example had been of a small amount of data obtained in animals by a different route of exposure, an uncertainty factor of 1000 might be applied.

Safety Margins

A safety margin is the difference or ratio between the allowable limit (after correction by the uncertainty factor) and the available dose. How large does a safety margin need to be? Generally, a safety margin of 100× or more is desirable, but this can depend on the security of the risk under consideration, the type of product, the business risk to the company, and the potential benefits of product use (Tables 4.18 and 4.19).

TABLE 4.18
ISO 10993 (Most Recent Revisions)

ISO 10993 Consists of the Following Parts, under the General Title *Biological Evaluation of Medical Devices*

Part 1: Evaluation and testing (2009)
Part 2: Animal welfare requirements (2006)
Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity (2014)
Part 4: Selection of tests for interactions with blood (2013)
Part 5: Tests for cytotoxicity: *in vitro* methods (2009)
Part 6: Tests for local effects after implantation (2007)
Part 7: Ethylene oxide sterilization residuals (2008)
Part 8: Guidance for reference materials (no longer operative)
Part 9: Framework for the identification and quantification of potential degradation products (2009)
Part 10: Tests for irritation and sensitization (2010)
Part 11: Tests for systemic toxicity (2006)
Part 12: Sample preparation and reference materials (2012)
Part 13: Identification and quantification of degradation products from polymers (2010)
Part 14: Identification and quantification of degradation products from ceramics (2001)
Part 15: Identification and quantification of degradation products from metals and alloys (2000)
Part 16: Establishment of allowable limits for leachable substances (2012)
Part 17: Chemical characterization of materials (2005)
Part 18: Physicochemical, mechanical, and morphological characterization (2006)

Note: Future parts will deal with other relevant aspects of biological testing. Note that EN 14971 (2012) covers device risk assessment.

TABLE 4.19
An Overview of the Classification of Medical Devices (Rules 1–12)

Class	Noninvasive Devices				Invasive Devices				Additional Rules for Active Devices			
						Surgically Invasive Devices						
	Others	Channeling or storing substances for introduction into the body	Biological or chemical modification of liquids for infusion	Contact with injured skin	Body Orifices	Transient use	Short-term use	Long-term use, implantable devices	Therapeutic devices for administration or exchange of energy	Diagnostic devices to supply energy, vital physiological processes; radio-pharmaceutical imaging	Devices for administration or removal of substances to or from the body	Others
I	Regular	Regular		Mechanical Barrier; compression; absorption of exudates	Transient use; ENT short-term	Reusable surgical instruments				Illumination of human body in visible spectrum		Regular
IIa		Body substances; connections to AMD ≥ IIa	Filtration; centrifugation; gas or heat exchange	Regular	Short-term use ENT, long-term Connection to AMD ≥ IIa	Regular	Regular	Placed in teeth	Regular	Regular	Regular	
IIb			Regular	Wounds with breached dermis, healing by secondary intent	Long-term use	Ionizing radiation; biological effect; absorbed; potential hazard of medicine delivery system	Ionizing radiation; chemical change (except in teeth); medicine administration	Regular	Potentially hazardous (nature, density, site of energy); Class IIb ATD monitor control development	Immediate danger to heart, respiration, CNS; Ionizing radiation including control monitoring	Potentially hazardous (substances, part of body, mode of applications)	
III						Heart; CCS	Heart; CCS; CNS; biological effect; absorbed	Heart; CCS; CNS; biological effect; absorbed; chemical change; medicine administration				
Rule	1	2	3	4	5	6	7	8	9	10	11	12

Key: AMD, Active Medical Device; ATD, Active therapeutic device; CCS, Central circulatory system; CNS, Central nervous system; ENT, ear nose and throat.

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5 Food Additives and Nutrition Supplements

Chada S. Reddy and A. Wallace Hayes

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In the early twentieth century, Harvey Wiley of the United States Department of Agriculture and others led an effort to put an end to food adulteration and to provide regulatory authority to the federal government. The resulting Pure Food and Drugs Act of 1906 made illegal any food found to be adulterated (contained an "added impure or...deleterious ingredient"), which may render the food injurious to health. The government, however, had the burden of proof of adulteration and that there was a reasonable (not absolute) possibility that harm might result. This meant that, since the injurious effects of most food adulterants in human beings are not known, results from studies in experimental animals could be used to make conclusions regarding the possibility of harm to human beings.

Subsequent understanding that animal studies could predict possible adverse effects not already recognized in humans, combined with the advent of more accurate and sensitive analytical instruments led, in the mid-twentieth century, to a series of amendments to the federal food safety laws. The resulting watershed legislation, the Food, Drug, and Cosmetic Act (FDCA) of 1938, required manufacturers to prove the safety of any product that would be marketed over state lines, and provided for three kinds of food standards: (1) standards (definitions) of identity, (2) standards of quality, and (3) standards regulating the fill of container. As defined in the FDCA, a food is considered to be adulterated if it contains any added poisonous or deleterious substance that may *render it injurious to health*. Adulteration is defined as a food that bears or contains any added poisonous or deleterious substance; or if it bears or contains a pesticide chemical residue, a food additive, or a new animal drug that is unsafe; or if it consists of or is contaminated by any other substance that makes it unfit for food or renders it injurious to health; or if its container is composed of any poisonous or deleterious substance that may render the contents injurious to health; or if it has been intentionally subjected to radiation not conforming with regulation. The act distinguishes, however, between substances naturally present and those that have been added to the food. If the substance is something that has not been added to the food, the food is not to be considered adulterated under this regulation if the quantity of this substance does not *ordinarily render it injurious to health*.

ROLE OF FOOD ADDITIVES IN THE DIET

The human diet is an exceedingly complex mixture and contains perhaps hundreds of thousands of structurally diverse chemical substances, most of natural origin. These include nutrients, color and flavor-imparting substances that are purposely added. Many more become components during the processes of food and beverage preparation-cooking, smoking, fermentation etc. —bring about many chemical changes and introduce compounds nor found in raw produces. Further, human beings add chemicals to achieve certain technical effects such as preservation, color, consistency (emulsify), flavoring, sweetening, and other physical effects. More chemicals are introduced, usually in very small amounts, as by-products of agriculture and packaging. Among these are crop-use pesticides, drugs used in food animal production, and substances that migrate from food contact surfaces and packaging. Finally, the diet also contains unwanted contaminants of both natural (bacterial and fungal metabolites) and industrial origin. This chapter deals predominantly with the safety assessment of those chemicals that are added to foods or become components of human diet secondary to contact with it during processing. Reviews of Frankos and Rodricks (2002) and of Kruger et al. (2014) serve as resources for much of the discussion presented in this chapter.

The Food Additive Amendment (1958) to the FDCA subjected the food additives to heavy regulatory scrutiny and allowed the Food and Drug Administration (FDA) the authority to require information from the manufacturers demonstrating that the food additive they intend to use is reasonably free of harm prior to its introduction into the food supply. Since that time, the FDA, with help from academia and industry, is continuously developing, sharpening and setting forth the types of

toxicity and chemistry studies needed and criteria to assess the safety of food additives. The objectives of this chapter are to summarize these requirements in the US and to provide some guidance on how they are to be met.

The FDCA recognizes three broad categories of food constituents (Roberts, 1981) and imposes substantially different regulatory and technical requirements upon them:

1. Substances intentionally added to food, both directly and indirectly
2. Substances that are natural components of food
3. Substances that may contaminate food

The regulation of a substance in the food supply depends upon the intended use and the claims made for the product. Food is consumed for taste, aroma, and nutritive value. A new product may be regulated as a food additive or generally recognized as safe (GRAS) ingredient if the intent is for it to become a component of or affect the characteristics of a food. Substances that are directly or indirectly added to food (of which there are several subgroups) can be legally introduced only if they have been shown by the manufacturer to be free from adverse effects under the conditions of use. A food additive that is capable of and is intended to impart color when added or applied to a food is regulated separately as a color additive. If a dietary substance(s) is intended to be used by people to supplement the diet by increasing the total dietary intake, then the substance is regulated as a dietary ingredient. The supplement in which the dietary ingredient is contained, however, must not be represented for use as a conventional food or as a sole item of a meal or the diet.

The implications for the safety evaluation and risk assessment process needed to ensure compliance with the applicable regulations for food and color additives, GRAS ingredients, and new dietary ingredients (NDIs)/dietary supplements will be discussed further in this chapter. The FDA developed a decision tree (Figure 5.1), which utilizes information on intended use and existing authorizations to determine the regulatory path for a food ingredient (http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm228269.htm). It is the responsibility of the manufacturer of any food to ensure that all ingredients used are of food-grade purity and comply with specifications and limitations in all applicable authorizations. The overall regulatory status of a food is affected by the regulatory status of each individual food ingredient. To determine compliance, each authorization must consider three elements: identity of the substance, specifications including purity and physical properties, and limitations on the conditions of use.

DIRECT AND INDIRECT FOOD ADDITIVES

Any substance that is reasonably expected to become a component of food is a *food additive*. Food additives are subject to premarket approval by the FDA, unless the substance is GRAS among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use or meets one of the other exclusions from the food additive definition in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Table 5.1 lists some representative food ingredients including currently approved direct and indirect food additives with examples.

Substances that are added to a food for a specific purpose are known as *direct additives*. For example, aspartame, the low-calorie sweetener, is a direct additive that is added to puddings, soft drinks, yogurt, and many other foods. Direct additives are identified on a food's ingredient label. *Indirect additives* become part of the food in very small amounts during the processing, packaging, or storage of the food item. In general, food additives serve a valuable technical function in food: (1) to maintain the nutritional quality of food; (2) to enhance keeping quality or stability, with resulting reductions in food wastage; (3) to make food attractive to consumers; and (4) to provide essential

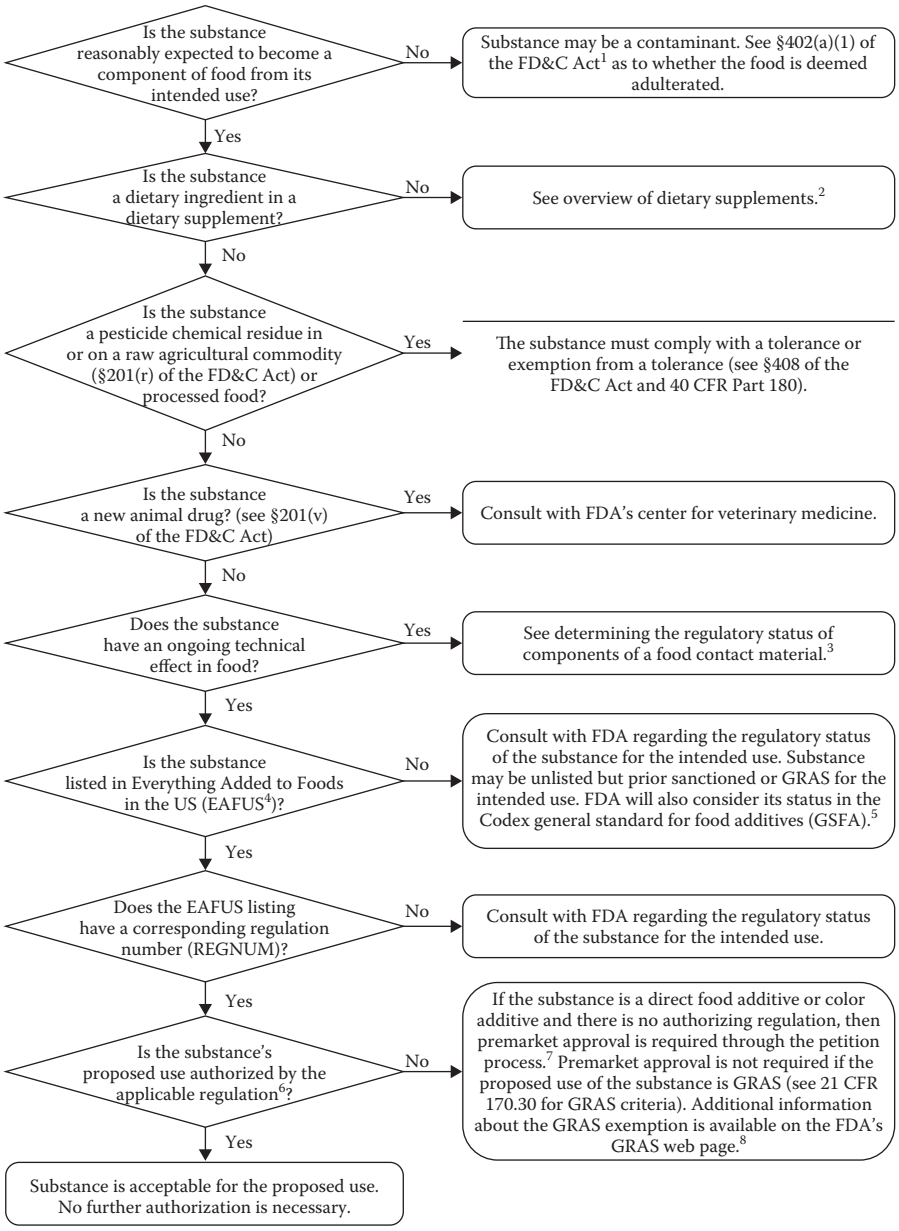

FIGURE 5.1 Food ingredient decision tree. [1]FFDCA, https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDAMA/FDAMAImplementationChart/ucm089259.htm; [2]overview of dietary supplements, http://www.fda.gov/Food/DietarySupplements/default.htm; [3]determining the regulatory status of components of a food contact material, http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/RegulatoryStatusFoodContactMaterial/ucm120771.htm; [4]everything added to food in the United States (EAFUS), http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing; [5]codex general standard for food additives (GSFA), http://www.codexalimentarius.net/gsfaonline/index.html;jsessionid=149CBF5BF97E536467770AEEBC15510D; [6]FDA's food and color additives regulations, http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm082463.htm; [7]petition process, http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm253328.htm; [8]GRAS, http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm. (From US FDA, Determining the regulatory status of a food ingredient.)

TABLE 5.1
Various Food Ingredients, Their Functions, Uses and Examples

Types of Ingredients	What They Do	Examples of Uses	Names Found on Product Labels
Preservatives	Prevent food spoilage from bacteria, molds, fungi, or yeast (antimicrobials); slow or prevent changes in color, flavor, or texture and delay rancidity (antioxidants); maintain freshness	Fruit sauces and jellies, beverages, baked goods, cured meats, oils and margarines, cereals, dressings, snack foods, fruits and vegetables	Ascorbic acid, citric acid, sodium benzoate, calcium propionate, sodium erythorbate, sodium nitrite, calcium sorbate, potassium sorbate, BHA, BHT, EDTA, tocopherols (Vitamin E)
Sweeteners	Add sweetness with or without the extra calories	Beverages, baked goods, confections, table-top sugar, substitutes, many processed foods	Sucrose (sugar), glucose, fructose, sorbitol, mannitol, corn syrup, high fructose corn syrup, saccharin, aspartame, sucralose, acesulfame potassium (acesulfame-K), neotame
Color additives	Offset color loss due to exposure to light, air, temperature extremes, moisture and storage conditions; correct natural variations in color; enhance colors that occur naturally; provide color to colorless and *fun* foods	Many processed foods, (candies, snack foods margarine, cheese, soft drinks, jams/jellies, gelatins, pudding, and pie fillings)	FD&C Blue Nos. 1 and 2, FD&C Green No. 3, FD&C Red Nos. 3 and 40, FD&C Yellow Nos. 5 and 6, Orange B, Citrus Red No. 2, annatto extract, beta-carotene, grape skin extract, cochineal extract or carmine, paprika oleoresin, caramel color, fruit and vegetable juices, saffron (Note: Exempt color additives are not required to be declared by name on labels but may be declared simply as colorings or color added)
Flavors and spices	Add specific flavors (natural and synthetic)	Pudding and pie fillings, gelatin dessert mixes, cake mixes, salad dressings, candies, soft drinks, ice cream, BBQ sauce	Natural flavoring, artificial flavor, and spices
Flavor enhancers	Enhance flavors already present in foods (without providing their own separate flavor)	Many processed foods	Monosodium glutamate (MSG), hydrolyzed soy protein, autolyzed yeast extract, disodium guanylate or inosinate
Fat replacers (and components of formulations used to replace fats)	Provide expected texture and a creamy *mouth-feel* in reduced-fat foods	Baked goods, dressings, frozen desserts, confections, cake and dessert mixes, dairy products	Olestra, cellulose gel, carrageenan, polydextrose, modified food starch, microparticulated egg white protein, guar gum, xanthan gum, whey protein concentrate
Nutrients	Replace vitamins and minerals lost in processing (enrichment), add nutrients that may be lacking in the diet (fortification)	Flour, breads, cereals, rice, macaroni, margarine, salt, milk, fruit beverages, energy bars, instant breakfast drinks	Thiamine hydrochloride, riboflavin (Vitamin B_2), niacin, niacinamide, folate or folic acid, beta carotene, potassium iodide, iron or ferrous sulfate, alpha tocopherols, ascorbic acid, Vitamin D, amino acids (L-tryptophan, L-lysine, L-leucine, L-methionine)

(*Continued*)

TABLE 5.1 (*Continued*)
Various Food Ingredients, Their Functions, Uses and Examples

Types of Ingredients	What They Do	Examples of Uses	Names Found on Product Labels
Emulsifiers	Allow smooth mixing of ingredients, prevent separation Keep emulsified products stable, reduce stickiness, control crystallization, keep ingredients dispersed, and to help products dissolve more easily	Salad dressings, peanut butter, chocolate, margarine, frozen desserts	Soy lecithin, mono- and diglycerides, egg yolks, polysorbates, sorbitan monostearate
Stabilizers and thickeners, binders, texturizers	Produce uniform texture, improve *mouth-feel*	Frozen desserts, dairy products, cakes, pudding and gelatin mixes, dressings, jams and jellies, sauces	Gelatin, pectin, guar gum, carrageenan, xanthan gum, whey
pH control agents and acidulants	Control acidity and alkalinity, prevent spoilage	Beverages, frozen desserts, chocolate, low acid canned foods, baking powder	Lactic acid, citric acid, ammonium hydroxide, sodium carbonate
Leavening agents	Promote rising of baked goods	Breads and other baked goods	Baking soda, monocalcium phosphate, calcium carbonate
Anti-caking agents	Keep powdered foods free-flowing, prevent moisture absorption	Salt, baking powder, confectioner's sugar	Calcium silicate, iron ammonium citrate, silicon dioxide
Humectants	Retain moisture	Shredded coconut, marshmallows, soft candies, confections	Glycerin, sorbitol
Yeast nutrients	Promote growth of yeast	Breads and other baked goods	Calcium sulfate, ammonium phosphate
Dough strengtheners and conditioners	Produce more stable dough	Breads and other baked goods	Ammonium sulfate, azodicarbonamide, L-cysteine
Firming agents	Maintain crispness and firmness	Processed fruits and vegetables	Calcium chloride, calcium lactate
Enzyme preparations	Modify proteins, polysaccharides and fats	Cheese, dairy products, meat	Enzymes, lactase, papain, rennet, chymosin
Gases	Serve as propellant, aerate, or create carbonation	Oil cooking spray, whipped cream, carbonated beverages	Carbon dioxide, nitrous oxide

Source: US FDA, *Overview of Food Ingredients, Additives and Colors*, 2014.

aids to processing. By law, manufacturers must document that the amounts present are below the threshold of observable adverse effects. At present, there are thousands of food additives most being of indirect nature. These substances have been the subject of *food additive petitions* submitted to the FDA since 1958. These food additive petitions contain all information pertaining to safety and were found adequate by the Agency to meet its criteria for approval.

Legal Burdens for Proof of Safety

The Food Additive Amendments of 1958 stipulates that the manufacturers (*petitioners*) must satisfy the FDA's safety criteria prior to the marketing of a food additive. The safety standard is defined as "reasonable certainty in the minds of competent scientists that a substance is not harmful under its intended conditions of use." The FDA's role is to specify the safety criteria and the type and quantity of the data necessary to satisfy these criteria, although petitioners certainly have a major role in decisions regarding the types of data appropriate in specific cases. In addition to information on an additive's chemistry and purity, the FDA requires information on its intake by humans from its proposed uses and on its toxicity in experimental animals. No clinical studies in humans are required. The FDA's goal is to ensure an adequate margin of safety between the expected level of human intake and the exposure levels that produce adverse health effects in animals. Any food additive that is intended to have a technical effect in the food is deemed unsafe, under section 409 of the act, unless it conforms to the terms of its approved use or to an exemption for investigational use. Any food that contains an unsafe food additive is adulterated undersection 402(a)(2)(C) of the FFDCA.

The Delany Amendment

The Delaney clause, enacted in 1958 as part of the Food Additives Amendment, states:

> *No additive shall be deemed safe if it is found to induce cancer when ingested by man or animal or, if it is found after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.*

This is based on the judgment by the US Congress that no food additive is likely to offer benefits sufficient to outweigh any risk of cancer. Although guidance on the enforcement of this controversial amendment is quite clear with respect to exclusion of carcinogenic direct food additives, FDA regulates indirect additives and manufacturing by-products based on the quantitative risk assessment discussed in the following.

GUIDE TO SAFETY ASSESSMENT ("THEREDBOOK")

Principles of Safety Evaluation

The FDA's currently preferred approach to safety assessment of food additives is compiled in a publication entitled *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food,* commonly known as *the Redbook*. It was originally published in 1982 (US FDA, 1982) and is currently under revision. Subsequent revision in Redbook II (1993) and others (US FDA, 2007) was part of the FDA's attempt to harmonize its toxicity testing guidelines with those published by other agencies, countries, and international organizations. It did not change the overall approach described the Redbook I and Redbook II, which is still organized around four basic principles. First, the Agency presumes that some toxicological information is necessary for every food additive. Second, the amount of safety data required for a particular food additive is dictated by what is called a *level of concern* (LOC). Third, the LOC is based on the magnitude of potential human intake of an additive and its molecular structure: exposure data carrying greater weight than that of the structure alert. The fourth premise is that the initial evaluation of testing

requirements by the Agency can be adjusted when toxicological data suggest that a significant or unexpected adverse effect is found to be associated with the ingestion of a particular additive. The results from toxicology studies are then utilized to calculate the Acceptable Daily Intake (ADI) which is then compared to the Estimated Daily Intake (EDI). If the EDI is less than the ADI, the food additive is determined to be safe under the proposed conditions of use.

A food additive petition (FAP) to the FDA requesting the approval of an additive contains, at a minimum, the following elements: (http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm253328.htm):

- The identity and composition of the additive
- Proposed use
- Use level
- Data establishing the intended effect
- Quantitative detection methods in the food
- Estimated exposure from the proposed use (in food, drugs, cosmetics, or devices, as appropriate)
- Full reports of all safety studies
- Proposed tolerances (if needed)
- Environmental information (as required by the National Environmental Policy Act [NEPA], as revised [62 FR 40570; July 29, 1997])
- Ensure that consistent information is presented throughout all sections of the petition, including those pertaining to
- Chemistry
- Toxicology
- Environmental science
- Any other pertinent studies (e.g., microbiology)

Levels of Concern—Direct Food Additives

The concept of *level of concern* (LOC) is fundamental to the safety assessment for direct food additives, aiding in the determination of the extent of testing needed in each case and in cost/time saving. The LOC is a predictive measure of hazard a particular additive may present and is subject to revision if initial data indicate otherwise. The levels of concern for various anticipated intakes of direct food additives, as given in Redbook II, are presented in Figure 5.2. A compound is first assigned a level of expected toxicity based on its molecular structure. These levels are designated by category: A (low toxicity), B (moderate toxicity), or C (high toxicity). The structure category assignment is based on answers to questions in a decision tree (Redbook II) related to the additive's chemical structure, the number and volume of unidentified components in the food additive, and its predicted metabolites. If fewer than 90% of the components of the additive have been structurally characterized, the additive is automatically placed into the highest toxicity category C. Examples of compounds in category A (low toxic potential) include: simple aliphatic, acyclic and monocyclic hydrocarbons; fats; fatty acids; simple aliphatic and non-cyclic (saturated) mono-functional alcohols; ketones; aldehydes; acids; esters; ethers; and normal human metabolites of carbohydrates and lipids. Category B (moderate toxic potential) compounds include: non-conjugated olefins (excluding unsaturated fatty acids and fats); inorganic salts of iron, copper, zinc and tin; amino acids; polypeptides; and proteins. Category C (toxicity likely high) compounds are structurally varied and include organic halides; amides and imines; conjugated alkenes; polycyclic aromatic hydrocarbons; and compounds with nitro, N-nitroso, azide, and purine groups.

Following categorization based on structure, a LOC is derived based on the anticipated human intake (Figure 5.2) of the compound. The Redbook lists groups of studies that are then required, as a minimum, to support its safety assessment (Table 5.2) for compounds in each of the concern

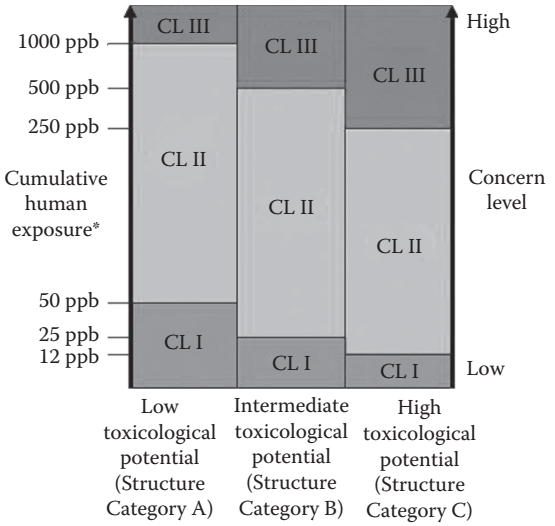

FIGURE 5.2 Concern levels (CL) as related to human exposure and chemical structure. * Cumulative human exposure is expressed as parts per billion (ppb, equivalent to microgram per kg diet) of daily dietary consumption of additives. Conversion of ppb to microgram per kg-body weight per day, divide by 20, assuming 3 kg daily diet. (From US FDA, Guidance to the industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations, US Government Press, Washington, DC, December 2007.)

TABLE 5.2
Recommended Toxicological Tests for Additives Used in Food

Toxicity Tests	Concern Level Low (I)	Level Intermediate (II)	Concern Level High (III)
Genetic toxicity tests	X	X	X
Short-term toxicity tests with rodents	X[c]	X[a,c]	X[a,c]
Subchronic toxicity studies with rodents		X[c]	X[a,c]
Subchronic toxicity studies with non-rodents		X[c]	X[a,c]
One-year toxicity studies with non-rodents			X[c]
Chronic toxicity or combined chronic toxicity/carcinogenicity studies with rodents			X[c]
Carcinogenicity studies with rodents			X
Reproduction studies		X[c]	X[c]
Developmental toxicity studies		X[b,c]	X[b,c]
Metabolism and Pharmacokinetic studies (available in 1993 Draft Redbook II)		X[b]	X[b]
Human studies			X[b]

[a] If needed as preliminary to further study.
[b] If indicated by available data or information.
[c] Including screens for neurotoxicity and immunotoxicity (available in PDF in 1993 Draft Redbook II).

levels I, II, and III. A compound with a Concern Level I requires only maximal testing including a short-term feeding study (at least 28 days in duration) in a rodent species and short-term tests for carcinogenic potential. Assignment to Concern Level II requires testing in a 90-day feeding study in a rodent and non-rodent species, a multigeneration reproduction study with a developmental toxicity phase in rodent species, and a battery of short-term tests for carcinogenic potential. A compound assigned to Concern Level III is required to undergo the most extensive testing, requiring, in addition to the studies required for a Concern Level II substance, carcinogenicity studies in two rodent species, a chronic feeding study of at least 1 year in duration in a rodent species, a multi-generation reproduction study with teratology phase in a rodent species, a nonrodent long-term feeding study, and short term tests for carcinogenic potential. These testing requirements may be modified as initial data dictates.

Threshold of Regulation Exemption—Indirect Food Additives (Food Contact Substances)

A food contact substance (FCS) is any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food. Under 21 CFR §170.39, the FDA states that if it can be demonstrated that a substance used in a food-contact article that may be expected to migrate into food results in a dietary concentration of that substance at or below 0.5 ppb (corresponding to dietary exposure levels at or below 1.5 μg/person/day), then the FDA will consider that substance to present no health or safety concern. Consequently, this substance will be exempt from regulation as a food additive because it becomes a component of food at levels that are below the Threshold of Regulation (*TOR*). *Known carcinogens are not exempt*. This regulatory option requires that the information on which the TOR exemption claim is based be submitted to the FDA for review. If the FDA concurs with the TOR analysis, the substance will be added to the list of approved TOR exemptions that is maintained by the Agency and is publicly available. Premarket approval of all FCS is required unless exempted.

Food Contact Substance (Indirect Food Additive) Notification

In 1997, the Food and Drug Administration Modernization Act of 1997 (FDAMA) established a food contact notification (FCN) process to allow faster review of non-exempt FCS. Food contact notification, because of similar safety standard to a petition, must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification is safe for the intended use (21U.S.C.348(h)(l)). Regardless of whether a FCN or petition is submitted, the following information is required in addition to relevant information outlined in the direct food additive petition earlier:

- Migration (extraction) data. Complete requirements, including extraction methodologies, are found in the FDA guidance document entitled, *Recommendations for Chemistry Data for Indirect Food Additive Petitions* June 1995) and *Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations* (US FDA, 1999b)
- Full reports of investigations made with respect to the safety of the additive, both published and unpublished
- Evaluation of the safety of consumption of residues/extractables from the additive including determination of an Acceptable Daily Intake (ADI) for the additive itself, calculations of its Estimated Daily Intake (EDI) in the total diet, and a comparison of the EDI to the ADI

Very recently the FDA amended the food additive regulations to no longer provide for the use of three specific perfluoroalkyl ethyl containing FCSs as oil and water repellants for paper and paperboard for use in contact with aqueous and fatty foods. This was based on new data showing that safety profiles of structurally similar compounds suggest that there is no longer a reasonable certainty of no harm from the food-contact use of these FCSs. This action was in response to a petition filed by the Natural Resources Defense Council, the Center for Food Safety, the Breast Cancer Fund, the Center for Environmental Health, Clean Water Action, the Center for Science in the Public Interest, Children's Environmental Health Network, Environmental Working Group, and Improving Kids' Environment (US FDA, 2016a).

Estimated Daily Intake

Direct Food Additives

Petitioners are required to provide data that would allow a reliable estimation of the daily human intake of the additive, the EDI. The EDI is determined by multiplying the dietary concentration of the additive by the total weight of food consumed by an individual per day (3,000 g). For direct additives, the concentration of the additive is recommended by the petitioner, to be later approved by the FDA, for each of the additive's technical applications. The estimated *all-person* and *all-user* total intakes of ingredient from all proposed food uses in the United States by population group is summarized thus generating the EDI by gender and age group, and as appropriate for comparison with the ADI, generating the safety assessment for the ingredient. The goal is to ensure that the EDI for the 90th percentile consumer of foods or beverages in which the additive will be present falls below the ADI. Thus, for each dietary item that may contain the additive, data on the additive's maximum concentration and on human consumption rates for the food item, including that for the 90th percentile consumer, must be presented. If the EDI does not exceed the ADI, the additive is approvable. The process of EDI determination for direct food additives, as described in the following, is detailed by Kruger et al. (2014).

In dietary intake assessments, the concentration of an ingredient or chemical constituent in food can be obtained from the intended use levels of the substance in target foods (typical, recommended, or maximum use level); the measured concentration in food as consumed, accounting for processing and storage losses of ingredient; the limit of detection (LOD) or limit of quantification (LOQ) of the analytical method, as appropriate, if the concentration in the food is non-detectable or non-quantifiable at the LOD or LOQ; established limits for the substance (e.g., specifications in the CFR or the Food Chemical Codex [FCC]), for undesirable impurities and contaminants in food ingredients; or maximum levels for contaminants in foods adopted by a recognized standards-setting body, such as the Codex Alimentarius Commission. The FDA typically uses the maximum intended use levels proposed to calculate a *worst-case* level of intake.

The FDA relies primarily on food consumption surveys as sources of data available for use in estimating intake of substances in the diet.

Food Consumption Surveys

The FDA regularly uses nationwide food consumption surveys at the individual level to collect information on mean food intakes and the distribution of food intakes within subpopulations of individuals defined by demographic (age, etc.) factors and health status (pregnancy, lactation, etc.). One or more methods including food records or diaries, 24-hour recalls, food frequency questionnaires (FFQ), and diet history are used.

The US Department of Agriculture (USDA) also frequently collects nationwide food consumption data (USDA, 1997; continuing Survey of Food Intake by Individuals, CSFII), which, over time, transformed into the National Health and Nutrition Examination Survey (NHANES) survey

collecting data annually to measure the knowledge and attitudes about nutrition, diet and health. NHANES became a continuous program in 1999, with approximately 5,000 individuals surveyed each year (NHANES I, II, and III). NCHS released data sets to the public in 2-year cycles (NCHS, 1999–2000, 2001–2002). These dietary data are released in two files: a total nutrient intakes file and an individual food file (with detailed records of gram weights and nutrient values). Beginning in January 2002, NHANES studies collect data on two non-consecutive 1-day recalls, the most recent of which involving 10,000 people for the years 2009–2010 are available for public use: http://wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx. Consecutive years of data collection is a nationally representative sample of the US population. It is well established that the length of a dietary survey affects the estimated consumption of individual users, and that short-term 1-day dietary survey over estimates consumption over longer time periods (Gregory et al., 1995). In addition to collecting information on the types and quantities of foods being consumed, NHANES (NCHS, 2009–2010) survey collected participants' socioeconomic, physiological, and demographic information, such as sex, age, height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population.

Estimates for the daily intake of ingredient represent projected 2-day averages for each individual from day 1 and day 2 of the NHANES (NCHS, 2009–2010) data. Mean and percentile estimates are generated incorporating sample weights in order to provide representative intakes for the entire US population. All-person intake refers to the estimated intake averaged over all individuals surveyed, regardless of whether they consumed food products containing the ingredient, and therefore includes zero consumers (those who reported no intake of the food products containing the ingredient during the two survey days). All-user intake, a better estimate, refers to the estimated intake by those individuals consuming food products containing the ingredient. Individuals are considered users if they consumed one or more food products containing the ingredient on either day 1 or day 2 of the survey. The individual proposed food uses, default serving sizes, and the corresponding maximum-use levels for specific foods, as identified by food codes representative of each proposed use, are chosen from the Food and Nutrition Data base for Dietary Studies (FNDDS). In FNDDS, the primary (usually generic) description of a given food is assigned a unique eight-digit food code (CDC, 2006; USDA, 2012). FDA Guidance for Industry: Estimating Dietary Intake of Substances in Food can be found at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm074725.htm#mode.

Food Contact Substances

The EDI for indirect additives (such as FCS) is calculated using methods outlined in the FDA's Recommendations for Chemistry Data for Indirect Food Additive Petitions and FDA's Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations (US FDA, 1999b). The EDI is based on a calculation of the amount of additive that could potentially migrate from the food-contact material into various foods, and a subsequent calculation of the amount of those foods that would be consumed by a person each day. Other uses of the additive will be added to the calculated EDI to estimate the Cumulative EDI (CEDI). The FDA uses the CEDI to assign a LOC to the compound that is the subject of the petition. The LOC determines the extent of toxicological testing needed for approval.

The type and amount of toxicological testing (both animal and *in vitro* studies) necessary for approval are specified in the FDA guidance entitled "*Preparation of Premarket Notifications for Food Contact Substance: Toxicology Recommendations*" (US FDA, 1999c). The FDA uses the concept of *level of concern* (LOC) in determining how much testing is necessary. For indirect additives, the LOC is based solely on anticipated human exposure. The Agency recommends that

the following toxicology studies be performed to assess the safety of a FCS (and its constituents if appropriate) with the indicated CEDIs:

1. CEDI <0.5 ppb (<1.5 μg/day): No toxicity studies are recommended for a FCS or constituent with an estimated CEDI less than 0.5 ppb. However, available information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in a Comprehensive Toxicological Profile (CTP).
2. CEDI >0.5 and <50 ppb (>1.5 to <150 μg/day): The potential carcinogenicity of food contact substances and their constituents should be evaluated using genetic toxicity tests. The recommended genetic toxicity tests include: a test for gene mutation in bacteria and an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma thymidine kinase (TK) assay. Other available information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in CTPs.
3. CEDI >50 ppb and <1 ppm (>150 to <3000 μg/day): The potential carcinogenicity of food contact substances and/or their constituents with estimated CEDI greater than 50 ppb but less than l ppm should be evaluated using genetic toxicity tests. The recommended genetic toxicity tests include an *in vivo* test for chromosomal damage using rodent hematopoietic cells in addition to those described for concern level 2 earlier. Other available information on the potential carcinogenicity and an estimate of the potential human risk (if any) due to the proposed use of the substance should be discussed in CTPs.

   The potential toxicity of a FCS and its constituents should be evaluated by two subchronic oral toxicity tests, one in a rodent species and one in a non-rodent species to provide an adequate basis for determining an ADI and to help determine the need for longer-term or specialized toxicity tests (e.g., metabolism studies, teratogenicity, reproductive toxicity, neurotoxicity and immunotoxicity studies).
4. CEDI >1 ppm (>3000 μg/day): The Agency requires that a food additive petition be submitted for the food contact substance.

Estimating Cumulative Estimated Daily Intakes

Estimates of indirect additive intake are usually derived by extraction studies with food-simulating solvents as described in the Recommendations for Chemistry Data for indirect Food Additives Petitions (US FDA, 1988) and the FDA's Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations (US FDA, 1999b).

The design of the extraction experiments is discussed in detail in the FDA guidelines (US FDA, 1988, 1998, 1999a) and includes consideration of the type of extraction vessel used, the concentration of the sample used in the extraction study, the thickness and surface area of the sample extracted, the volume of extracting solvent, the conditions of the extraction (the food stimulant used), the time and temperature of the extraction, and the characterization of the substance extracted. Efforts should be made to mimic the use of the indirect additive. The FDA guidelines recommend that 3% ethanol be used to simulate extraction into both aqueous and acidic foods, that 8% or 50% ethanol be used for alcoholic foods, and that food oils (such as corn oil) be used to simulate extraction into fatty foods. The guidelines also list certain specific polymers and the fatty-food simulants that it considers appropriate.

The migration data gathered using the FDA guidelines are intended to provide estimates of the higher level of migration to foods that might result from use of the new directive. Once applicable extraction data have been gathered, the values are used to calculate exposure to the additive, an estimate that depends not only on the extent of migration into food but also on the fraction of

TABLE 5.3
Consumption Factors (CF)

	Package Category	CF	Package Category	CF
A. General	Glass	0.1	Adhesives	0.14
	Metal-polymer coated	0.17	Retort pouch	0.0004
	Metal-uncoated	0.03	Microwave susceptor	0.001
	Paper-polymer coated	0.2	All Polymers[a]	0.8
	Paper-uncoated and clay-coated	0.1	Polymer	0.4
B. Polymer	Polyolefins	0.35[b]	PVC	0.1
	-LDPE	0.12	-rigid/semirigid	0.05
	-LLDPE	0.06	-plasticized	0.05
	-HDPE	0.13	PET[c,d]	0.16
	-PP	0.04	Other polyesters	0.05
	Polystyrene	0.14	Nylon	0.02
	EVA	0.02	Acrylics, phenolics, etc.	0.15
	Cellophane	0.01	All others[e]	0.05

Source: US FDA, Guidance to the Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations, December 2007.

[a] Originates from adding CFs for metal-polymer coated, paper-polymer coated, and polymer (0.17 + 0.2 + 0.4 = 0.8).

[b] Polyolefin films, 0.17 (HDPE films, 0.006; LDPE films, 0.065; LLDPE films, 0.060; and PP films, 0.037).

[c] PET-coated board, 0.013; thermoformed PET, 0.0071; PET carbonated soft drink bottles, 0.082; custom PET, 0.056; crystalline PET, 0.0023; PET films, 0.03.

[d] A CF of 0.05 is used for recycled PET applications (see the document entitled "Points to Consider for the Use of Recycled Plastics in Food Packaging: Chemistry Considerations").

[e] As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

a person's diet that is likely to contact materials containing the additive. The *Consumption Factor* (CF) is used to describe that portion of the diet likely to contact specific packaging materials. The FDA defines the CF as the ratio of the weight of food containing the specific packaging material to the weight of all goods packaged with that material. Examples of CF values used by the Agency for different packaging categories are shown in Table 5.3. The minimum CF used by the Agency is 0.05. As exemplified by the case of polystyrene, the CF, for which, was recently increased from 0.1 to 0.14. The CFs for the FCSs are frequently revised as dictated by the use pattern (Cassidy and Elyashiv-Barad, 2007).

Before the CF values can be used with the data on migration derived from extraction experiments to derive estimates of probable intake, information must be available on the nature (aqueous/acidic, alcoholic, fatty) of the food that will likely contact the packaging material. Food-type distribution factor(s) have been estimated by the Agency for each type of packaging material; they indicate the fraction of the food contacting each material that is aqueous/acidic, alcoholic, and fatty (Table 5.4). These values are then used along with the CF values and the migration data to estimate the expected migration (concentration) [M] of the new additive in food that contacts the packaging material, as follows:

$$[\mathrm{M}] = F_{\text{aqueous and acidi}c}\ (M_{10\%\text{EtOH}}) + F_{\text{alcohol}}(M_{50\%\text{EtOH}}) + F_{\text{fatty}}(M_{\text{corn oil or miglyol}})$$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying [M] by CF. The EDI is then determined by multiplying the dietary concentration ([M]) by the total weight of food consumed by an individual per day (3 kg or 3,000 g)

$$\text{EDI}\,(\text{mg/person per day}) = 3{,}000\ \text{g/person per day} \times [\mathrm{M}] \times \text{CF}$$

TABLE 5.4
Food-Type Distribution Factors (f_T)

	Package Category	Food-Type Distribution (f_T)			
		Aqueous[a]	Acidic[a]	Alcoholic	Fatty
A. General	Glass	0.08	0.36	0.47	0.09
	Metal-polymer coated	0.16	0.35	0.40	0.09
	Metal-uncoated	0.54	0.25	0.01[b]	0.20
	Paper-polymer coated	0.55	0.04	0.01[b]	0.40
	Paper-uncoated and clay-coated	0.57	0.01[b]	0.01[b]	0.41
	Polymer	0.49	0.16	0.01[b]	0.34
B. Polymer	Polyolefins	0.67	0.01[b]	0.01[b]	0.31
	Polystyrene	0.67	0.01[b]	0.01[b]	0.31
	-impact	0.85	0.01[b]	0.04	0.10
	-nonimpact	0.51	0.01	0.01	0.47
	Acrylics, phenolics, etc.	0.17	0.40	0.31	0.12
	PVC	0.01[b]	0.23	0.27	0.49
	Polyacrylonitrile, ionomers, PVDC	0.01[b]	0.01[b]	0.01[b]	0.97
	Polycarbonates	0.97	0.01[b]	0.01[b]	0.01[b]
	Polyesters	0.01[b]	0.97	0.01[b]	0.01[b]
	Polyamides (nylons)	0.10	0.10	0.05	0.75
	EVA	0.30	0.28	0.28	0.14
	Wax	0.47	0.01[b]	0.01[b]	0.51
	Cellophane	0.05	0.01[b]	0.01[b]	0.93

Source: US FDA, Guidance to the industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations, December 2007.

[a] For 10% ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.

[b] 1% or less.

The EDI is used together with information on exposure from all other uses of the indirect additive to establish the CEDI which is used to establish the level of toxicological testing that will be required for approval.

Toxicology Testing in Animals

The extent and types of toxicological studies required to support the safety of either direct or indirect food additives are dependent on both the EDI and the expected nature and potential for toxicity of the additive. Redbook II includes the following:

Short-Term Genetic Toxicity Studies

A modified battery including *Salmonella typhimurium* reverse mutation assay, *in vitro* mutagenicity in mammalian cells and *in vivo* cytogenetics.

Acute Oral Toxicity Studies

Results of acute oral toxicity study will provide information on the type of toxicity (e.g., neurotoxicity, cardiotoxicity), identify target organ(s), and dose levels for longer-term toxicity studies. The focus should be not on the number of animals that die at a given lethal dose, or LD_{50} determination, but rather the toxic effects on organ systems and the recovery of the animals from the administration of high doses of the test compound (Kokoski et al., 1990).

Short-Term Feeding Studies

Short-term studies generally last 28 days in duration, with multiple dose groups of animals exposed repeatedly to the chemical in their diets. This type of study is required for Concern Level I compounds and is useful for identifying the toxic characteristics and target organ(s) of an additive and as a range-finding study for sub-chronic and chronic studies to help set doses for these studies. Animals should be observed daily for overt signs of toxicity, and gross necropsies performed typically on all animals, including those that die during the course of the study.

Sub-Chronic Feeding Studies

Sub-chronic feeding studies are required for Concern Level II compounds and examine the toxicity (target organs, potency etc.) of a compound in greater detail after repeated dosing of at least three dose groups of 20 rodents or 4 dogs/gender/group animals generally for period of 90 days. Blood and urine sampling is performed periodically throughout the studies for determination of insidious toxicity and to aid in target organ identification. At termination of the study, detailed gross necropsies and histopathology are performed on representative test (high dose) and control animals. The tests are designed to mimic human exposure and may involve administration in the diet, through drinking water, in tablets, or by gavage. Redbook II recommends that screening for neurotoxicity and immunotoxicity be performed and that rodents be single-caged. Effects related to accumulation of the chemical in tissues become evident and the results should allow for determination of a *No Observable Adverse Effect* level. For a Concern Level III compound, the sub-chronic study helps dose selection for chronic study. For substances in Concern Levels I and II, data from sub-chronic tests are often used for the ultimate determination of safety (Kokoski et al., 1990; US FDA, 1988).

Reproductive and Developmental Toxicity Studies

Reproductive and developmental toxicity testing is required for compounds of Concern Levels II and III and are conducted by exposing male and female rodents (20/gender/group) orally to the additive to determine its effects on a variety of endpoints including male and female gonadal function, estrous cycles, mating behavior, conception, parturition, lactation, weaning, and growth and development of the off spring. The mechanisms of any effects elicited are rarely apparent from the results of such testing; however, the data do provide information on the effects of the chemical on neonatal morbidity and mortality and on the teratogenic potential of the test substance.

Three test levels and a control group are included for parental animals of both generations (P and F_1). The animals in both generations are treated before mating, during pregnancy, and through weaning of the F_1 offspring. Selected F_1 offspring are treated during their growth into adulthood, mating, production through weaning (21 days old) of an F_2 generation. For each generation, at least one litter should be examined. If toxicity is identified in the first litter, the study should then be expanded. Animals should also be screened for neurotoxicity and immunotoxicity. A detailed assessment of male reproductive effects is also included.

In a teratogenicity phase of any multi-generation study, the test substance must be administered during in-utero development. Multiple dose groups are also included as well as a control. The dams are killed 1 day before parturition. The uterus is removed and examined for embryonic or fetal deaths, live fetuses, and any evidence of malformations of skeletal or soft tissues. Ovaries are examined for the number of corpora lutea. Live fetuses are weighed, sexed, and examined for external abnormalities. A selected number of fetuses are examined for soft tissue malformations, usually by random selection of one-third of the group. The remaining two-thirds of the fetuses are examined for skeletal defects.

Chronic Toxicity and Carcinogenicity Studies

Chronic toxicity and carcinogenicity studies are required for a Concern Level III food additive and are often combined into one study. The studies are of lifetime duration in two rodent species lasting 104 weeks. The studies are usually designed to include several satellite groups for interim

kills at 3, 6, and 12 months to determine the compound-related effects that are not due to aging. The Redbook II also recommends using 50 animals/sex/group, single housing of rodents, periodic observation of the animals for signs of onset and progression of toxic effects, hematological and organ function tests, clinical examinations for neurological and ocular changes. Histopathology should be performed on all animals in the study.

Definitive evidence of carcinogenicity is difficult to establish from the results of a single study using a few dozen animals per group. Factors such as histological changes, sensitivity of the bioassay and variability in background tumor incidence must also be considered. Other correlative information (e.g., results from short-term genotoxicity testing, structure-activity relationships, dose-response relationships, the number of strain sand/or species tested, pharmacokinetic handling or metabolism of the compound, and the degree/site/incidence of the tumor response) is often used in the evaluation of the *weight of the evidence* of carcinogenic potential. Because the Delaney Amendment prohibits the use of carcinogenic food additives, the interpretation of carcinogenicity test results has an exceedingly important impact on the safety assessment process.

Human Data (Clinical Studies)

Unlike for human drugs, under the FDCA, there is no requirement for obtaining clinical safety data for food additives. Instead, the safety assessment process for food additives can rest solely on the results from experimental animal studies. In cases where human data are available, however, the data may be incorporated into the safety profile of the food additive. In cases where human intake is expected to be relatively large, petitioners may choose to conduct human studies after a thorough completion of the nonclinical evaluation. Clinical studies for certain macro-ingredient food additives (e.g., non-caloric fat substitutes), however, may be required because high intake of macro-ingredient in rodents have been shown to induce alterations in normal physiology, leading to spurious toxicological effects of no consequence to humans (Munro, 1990). Further, questions related to high levels of such additives reducing dietary caloric content and altering the micronutrient homeostasis are best answered in human studies.

Environmental Effects of Food Additives

A food additive can be introduced into the environment during its manufacture, use, or disposal. Ingested additives can enter the environment via sewage. Chemicals used to produce food additives also may be added to waste water treatment, manufacturing or processing plants. Other routes of introduction for food additives include solid waste disposal in landfills, composing of foods, and incineration of solid wastes. The National Environmental Policy Act (NEPA) dictates that the FDA assess the environmental implications of its regulatory decisions (CFR Part 25, April 26, 1985). Petitioners are therefore required to prepare an environmental assessment before the FDA will approve a food additive petition. Issues required to be addressed include the intended use; physical/chemical properties; degree of metabolism following use; environmental fate in air, water, and soil; predicted environmental concentrations; potential toxicological effects on aquatic and terrestrial species; and environmental implications of manufacturing and ultimate disposal by the consumer. Needed studies are determined by evaluating the potential environmental exposure and toxicity information available for the additive.

Levels of introduction, rates of incorporation into soil, and environmental fate are then collected to predict the final concentration of the additive in the relevant environmental media. When possible, processes that affect the transport and transformation of food additives are used when estimating the environmental concentration. Useful data for this assessment include chemical stability (hydrolysis, photolysis), biodegradability, and mobility in waste media (water solubility, oil sorption, volatility). Once the amount of substance released into the environment has been estimated,

the environmental assessment involves examination of available data on toxicity to animals, plants, and other organisms at the ecosystem level in each environmental compartment (air, freshwater, estuarine, marine, and terrestrial ecosystems). The toxicity database is then compared with the level of environmental exposure to arrive at an assessment of risk (Frankos and Rodricks, 2002).

HUMAN RISK ASSESSMENT

Acceptable Daily Intake

The calculation of an Acceptable Daily Intake (ADI) level for human consumption of food additives, as accepted worldwide, is generally as follows:

1. Most sensitive indicator (non-cancer effect) of toxicity [point of departure] is identified.
2. Threshold or highest No-Observed-Adverse-Effect Level (NOAEL) is identified for the effect.
3. The NOAEL is divided by a safety factor as discussed in the following to arrive at the ADI.

It is assumed that individuals can be exposed to a daily intake of an additive at levels up to its human threshold or ADI for their full lifetime without significant risk for non-cancer effects (Frankos and Rodricks, 2002). The NOAEL represents the threshold of effect applicable to experimental animals. The uncertainties representing species variability of response in human beings compared to animals and among individuals more sensitive than others are then adjusted by using safety factors. If the NOAEL is from a chronic toxicity study, the typical safety factor is 100 (10 for each of the two major sources of variability). If the NOAEL is from a sub-chronic toxicity study, and a chronic ADI is desired, an additional factor of 10 is introduced. If the NOAEL is from a developmental/reproductive toxicity study revealing a Type I affect, a factor of 1,000 may be used. The magnitudes of the *standard* safety factors can be altered in specific situations if the data are available to suggest human sensitivities or variabilities are larger or smaller than is suggested previously. Data from human clinical studies, particularly concerning metabolic profiles, may provide the basis for such determinations. The ADI approach is not used for carcinogens.

Carcinogens and Risk Assessment

The Delaney Amendment unambiguously prohibits the intentional and direct addition of carcinogens to food as well as the establishment of tolerances for such substances. Despite the questioning of the wisdom of this strict requirement from the scientific community and subsequent arguments (failed) by legal experts, FDA has no flexibility in the interpretation of the relevance of animal carcinogens to humans. The question of whether a component of a FCS is a food additive and, if such a component is carcinogenic whether it is subject to the Delaney Amendment requirements has been debated for a long time. An example of such a chemical is residual monomers such as vinyl chloride or acrylonitrile that may be found at low levels in polymers used as FCS.

The FDA has decided to use the risk assessment approach as a regulatory tool to deal with such agents. Migrants from FCS become food additives only if they can be detected in food. The FDA does not specify the detection limits or the analytical methods to be used for each compound. Instead, the Agency is satisfied if the petitioner uses methods capable of detecting residues at concentrations sufficient to create daily intakes corresponding to lifetime risk no greater than 1×10^{-6}. The FDA has applied this approach to deal with carcinogenic manufacturing by-products that are present as impurities in food additives. If the additive is not carcinogenic when tested, trace amounts of carcinogenic impurities are permitted if their lifetime cancer risks do not exceed the one in a million criterion (Frankos and Rodricks, 2002).

THE FOOD ADDITIVE PETITION

Once safety data have been gathered for a potential new food additive, a food additive petition is prepared according to guidelines found in Section 409(b)(2) of the FDCA. In general, five general areas of information must be presented in a petition.

1. The identity of the additive
2. The proposed use of the additive
3. The intended technical effect of the additive
4. A method of analysis for the additive in food
5. Full reports of all safety investigations that have been performed to support its use

In addition, a petitioner may be asked to submit a full description of methods, facilities, and controls used in the production of the additive, along with samples of the additive and of food in which the additive will be used. In the case of indirect additives, additional information on extraction and migration of the substance into foods will be required, as discussed earlier. Further details can be found in Section 409(b)(2) of the FDCA.

GENERALLY RECOGNIZED AS SAFE SUBSTANCES

Recent reviews on the GRAS substances include those of Frankos and Rodricks (2002) and Kruger et al. (2014) among others. Under the 1958 food additive amendments to the FDCA, any substance intentionally added to food is a food additive and is subject to premarket approval by FDA unless the use of the substance is generally recognized as safe (GRAS; the GRAS provision) (or otherwise excepted from the definition of food additive—e.g., color additive). Food ingredients that had long been in use prior to 1958 (baking soda, salt, pepper, vinegar, etc.) were exempted from the premarket testing and approval processes required for other food additives. They could be classified as GRAS based on a demonstration that they had common use in food. Substances could also be classified as GRAS through *scientific evaluation procedures*. The principal criterion for GRAS status is documentation that a substance is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (...or experience based on common use in food) to be safe under the conditions of its intended use." This, effectively, meant that the scientific safety standard to which a GRAS substance is held is comparable to that of a food additive (Kruger et al, 2011).

By 1961, FDA had amended its regulations to include a list of food substances that are GRAS under certain conditions of use (*the GRAS list*). During the 1960s, many manufacturers requested the FDA's opinion on whether their conclusions of GRAS status were justified and received *opinion letters*. In 1969, when the FDA removed cyclamate salts from its GRAS list because of safety questions, then-President Nixon directed the FDA to reexamine the safety of GRAS substances. In the 1970s, the FDA conducted rulemaking to establish procedures used for sponsors to petition the FDA for a GRAS affirmation substances of their interest. A Select Committee on GRAS Substances (SCOGS) conducted a *comprehensive review* of generally presumed GRAS substances and affirmed most of these substances as GRAS. However, it required a small number to be further tested and subject to petition and affirmation (SCOGS, 1981).

In 1997, FDA proposed to replace the GRAS affirmation petition process with a notification procedure (*GRAS notification*) to eliminate the resource-intensive rulemaking procedures. Effectively, this means that all future GRAS reviews are going to rely on *self-determinations* of GRAS status by the notifiers and the FDA may or may-not be informed of such a determination. The key elements of a GRAS review, as specified under sections 201(s) and 409 of the FD&C Act and the FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, continue to be: technical evidence of safety and a basis to conclude that this evidence is generally known and accepted.

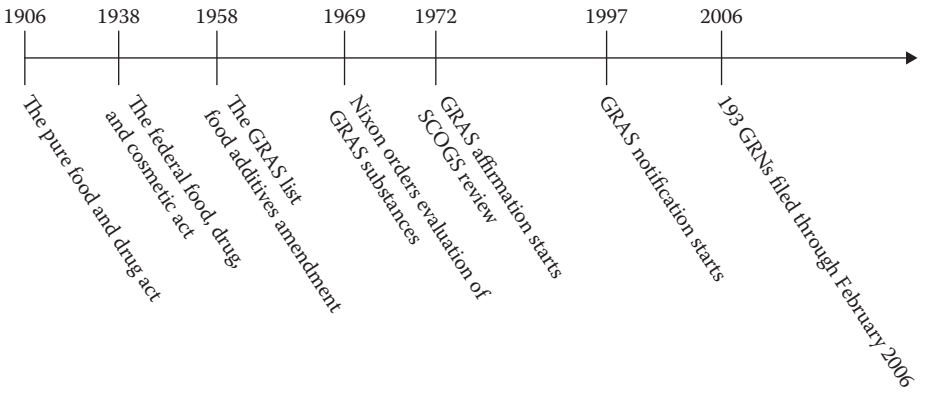

FIGURE 5.3 A GRAS timeline. (Adapted from http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/ucm094040.htm.)

Technical evidence can be derived from either scientific procedures or common use in food prior to January 1, 1958. Although the new GRAS notification process specifies both the format and scientific content of the submission to the FDA, the notification is not mandatory. In general, the FDA's response to a notification has been in one of three following categories:

- The agency does not question the basis for the notifier's GRAS determination.
- The agency concludes that the notice does not provide a sufficient basis for a GRAS determination (e.g., because the notice does not include appropriate data and information or because the available data and information raise questions about the safety of the notified substance).
- The response letter states that the agency has, at the notifier's request, ceased to evaluate the GRAS notice.

A summary of these events in the GRAS timeline is depicted in Figure 5.3.

The GRAS List

- 1958 food additives amendment: Congress recognized that many food substances would not require a formal premarket review by FDA to assure their safety.
- Food additives excludes substances that are recognized, among qualified experts, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food) to be safe under the conditions of their intended use.
- December 9, 1958: FDA published a list of GRAS substances and incorporated the list in Title 21 of the Code of Federal Regulations. The current list appears in 21 CFR Parts 182, 184, and 186.

Opinion letters

- Many manufacturers wrote to FDA and requested an opinion letter in which an FDA official would render an informal opinion on the GRAS status of use of the substance.
- Revoked in 1970 (21 CFR 170.6; 35 FR 5810; April 9, 1970).

Comprehensive review

- October 30, 1969: President Nixon directed FDA to make a critical evaluation of the safety of GRAS food substances.

- March 28, 1972: Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) began to summarize the available scientific literature and to recommend what restrictions, if any, on the use of the substances would be needed to ensure their safe use in food.

GRAS affirmation

- 1972: FDA conducted rulemaking to establish the procedures (21 CFR 170.35) that it would use to affirm the GRAS status of substances that were the subject of the GRAS review. That rule making included a mechanism (the GRAS affirmation petition process) where by an individual could petition FDA to review the GRAS status of substances not being considered as part of the agency's GRAS review.
- 1973–1997: GRAS affirmation petition process.

GRAS notification

- April 17, 1997: FDA proposed to establish a notification procedure whereby a person may inform FDA of a determination that the use of a substance is GRAS (62 FR 18938; April 17, 1997).
- Industry submits GRAS notice.
- FDA is evaluating whether each submitted notice provides a sufficient basis for a GRAS determination and whether information in the notice or otherwise available to FDA raises issues that lead the agency to question whether use of the substance is GRAS.

Safety Evaluation of Generally Recognized as Safe Substances

The information critical in determining the safety of a GRAS substance must be publicly available and includes at a minimum the following:

- *Description of the GRAS substance*: A review of the physical and chemical characteristics of the GRAS substance including chemical name(s) (and synonyms), CAS registry number(s), and chemical structure(s) and a description of final product characteristics including established food-grade specifications for the principal components, related substances, by-products, impurities and contaminants, and batch analysis results showing compliance with established food-grade specifications.
- *Production process*: Includes documentation of current good agricultural practice/current good manufacturing practice, detailed process flow diagram for each step of the production process and operation parameters, a list of raw materials and processing aids with food-grade and regulatory compliance documentation, critical control steps involved in the quality control process, description of potential impurities to be carried over to the final product, and documentation of stability and shelf life.
- *Historical use, regulatory status, and consumer exposure*: A review of the history of use and/or natural occurrence of the ingredient in other foods along with an intake or exposure estimate, current regulatory status if any, proposed use and use levels utilized to calculate the EDI of the GRAS substance.
- *Intended effect*: Intended function of the GRAS substance in the food.
- *Analytical methodology*: For determining the quantity of the substance in or on food, and any substance formed in or on food because of its use.
- *Review of safety data*: An evaluation of the actual use of the product and issues that may contribute to the safety of the product; critical review from the published animal toxicology and clinical literature for safety information on primary components, related substances, secondary metabolites, impurities, and contaminants using relevant data for occurrence

and/or levels present, estimated background intake, metabolic fate, toxicological activity, and pharmacological activity.
- *Safety assessment and GRAS determination*: Evaluation of the safety of consumption of the substance under its intended conditions of use including determination of an ADI for the substance as well as other components or contaminants and comparison of this ADI to the EDI of the substance from existing and proposed uses. As long as the EDI is less than (or approximately) the ADI, the substance can be considered safe under its intended conditions of use.

In addition to approximately 700 substances approved by the FDA, another >1,000 compounds independently affirmed by the FDA and accepted as GRAS by the Flavor and Extract Manufacturers Association (FEMA) are included in the GRAS list (Frankos and Rodricks, 2002). The largest numbers of compounds approved by the FDA are indirect additives, which are used to make paper and plastic packaging. Exposure to these compounds occurs through migration out of the packaging and, therefore, of an indirect nature. These compounds number in the thousands and are listed in 21CFR Parts 174–178. Although the FDA has published a list of GRAS substances, the agency realized it was impractical to list all substances that could be considered GRAS (Roberts, 1981). The FDA cannot withdraw an agent from the GRAS approval unless evidence appears showing that the substance is no longer safe for its intended use. New use of the substance, which result in an increased intake, must be justified by the manufacturers by self-affirmation of the GRAS status and notification to the FDA.

GENETICALLY MODIFIED FOODS

Kruger et al. (2014) provided a recent review of this topic. Existing conventional food crops and the products made from them, including those genetically modified or altered through conventional breeding/selection techniques to generate new varieties, are recognized to be safe. More recent technique of genetic engineering, process of removing a desirable gene from one organism or plant and transferring it to a different organism or plant allows plant breeders to achieve improvements in food crops such as resistance to pests and/or enhanced nutritional value (US FDA, 1999a). The new DNA introduced by genetic engineering produces a new protein the safety of which is evaluated as part of the risk assessment process. The substances intentionally added to food via biotechnology to date have been well-characterized proteins, fats, and carbohydrates and are functionally very similar to other proteins, fats, and carbohydrates that are commonly and safely consumed in the diet and so will be presumptively GRAS. The safety of a genetically engineered food crop or a product made from that crop is evaluated by comparing the nutritional and toxicological equivalence of the product to its conventional counterpart. Guidance for safety testing of genetically engineered products to assure that no unintended changes in the composition of the food could adversely affect human health has been published by authoritative scientific and regulatory agencies (Codex Alimentarius Commission, 2003; EFSA, 2006a, 2006b; Health Canada, 2006; ICMR, 2008; IFBC, 1990; US FDA, 1992). Differences between the conventional and bioengineered product are identified and the safety of the change is determined by additional experiments(US FDA, 1992, 1994).

The FDA provided guidance on the information that should be included in the safety and nutritional assessment (http://www.fda.gov/NewsEvents/Testimony/ucm115032.htm). Examples of such information are

- The name of the food and the crop from which it is derived.
- The uses of the food, including both human food and animal feed. The sources, identities, and functions of introduced genetic material.
- The purpose or intended technical effect of the modification, and its expected effect on the composition or characteristic properties of the food or feed.

- The identity and function of any new products encoded by the introduced genetic material, including an estimate of its concentration.
- Comparison of the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, anti-nutrients, and toxicants that occur naturally in the food.
- Information on whether the genetic modification altered the potential for the bioengineered food to induce an allergic response.
- Other information relevant to the safety and nutritional assessment of the bioengineered food.

If a bioengineered food included a new protein derived from an allergenic source and consumers would not expect it to be present based on the name of the food, the presence of that allergen must be disclosed on the label (US FDA, 2001). Because the FDA concludes that there is no basis to infer that foods developed by genetic engineering present any different or greater safety concern than foods developed by traditional plant breeding, labeling requirements for genetically modified foods are similar to conventional foods without the need to identify the 'genetically modified' nature of the product (US FDA, 1992). Support for this conclusion also comes not only from a number of studies (EFSA, 2003, 2004a, 2004b, 2006a, 2006b, 2007, 2008a, 2008b, 2009a–2009d, 2010a, 2010b, 2011a–2011e, 2012a–2012d), but also from a lack of documented evidence that any approved, commercially grown genetically engineered crop has caused allergic reactions related to the transgenic component (Goodman et al., 2008).

FOOD INGREDIENTS DERIVED FROM CHEMICALLY COMPLEX EXTRACTS

Natural products such as crude extracts, because of the presence of tens or hundreds of compounds at very low concentrations and because the matrix molecules can modify bioavailability and the toxic responses of the active components, render safety evaluation of individual compound impractical (IFT, 2009). An approach to determine the safety of natural products involves: a review and analysis of the existing phytochemical and botanical literature, establishing chemical composition of the raw material and the commercial product, determination of health-based levels of exposure for the identified compounds or compound, and utilization of published toxicology studies to establish safety of exposure to the extract through evaluation of the components/compound classes. A safety paradigm utilizing a thorough analytical elucidation of the composition of the complex natural product may allow a literature-based assessment of safety for the individual components/classes of compounds comprising the botanical extract. Traditionally, safety determination of a complex natural product has relied on animal toxicology testing. Similar to the definition, as described in the section 'Direct and Indirect Food Additives' section for food additives, in general, ADI—safe levels of ingestion of the complex mixture—can also be determined through the scientific procedures described in the Guide to Safety Assessment section. When the extract in the animals' diet exceeds 5% (w/w), however, the possibility that nutritional imbalance may contribute to the adverse effects observed must be considered (Booth et al., 2012; Hayes, 2008; Kruger and Mann, 2003; US FDA, 2003). In these cases, the concept of the 100-fold uncertainty (safety) factor is not appropriate in the determination of the ADI. Because the safety assessment of botanical substances is complicated by various factors including compositional diversity, lack of standardization of the botanical, lack of identity of the active ingredients, and the use of different formulations of the botanical in the article of commerce when compared with the test substance and/or its extracts, each new submission must be dealt with on a case-by-case basis (Abdel-Rahman et al., 2011).

COLOR ADDITIVES

Any substance that is added to food and imparts color to the food is a color additive (see color additive definition in section 201(t) of the FFDCA and 21 CFR 70.3(f) and the FDA's implementing regulations in 21 CFR Part 70). Under section 201(t)(1) and 21 CFR 70.3(f), the term color additive means a material that is a dye, pigment, or other substance made by a process of synthesis or

similar artifice, or extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source, and that is capable (alone or through reaction with another substance) of imparting color when added or applied to a food, except that such term does not include any material that the secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring. Under 21 CFR 70.3(g), a material that otherwise meets the definition of color additive can be exempted from that definition on the basis that it is used or intended to be used solely for a purpose or purposes other than coloring, as long as the material is used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. Any color additive in food is deemed unsafe unless its use is either permitted by regulation or exempted by regulation. In general, however, the safety criteria for color additives are identical to those used for food additives. Unlike the definition for food additive, however, there is no GRAS exemption for color additives and they are subject to additional legal requirement (e.g., batch-by-batch certification by the FDA for synthetic colors) not found in the food additive regulations. Any food that contains an unsafe color additive is adulterated under section 402(c) of the FFDCA.

Following the passage of the Color Additive Amendment of 1960, 20 natural colors (comprising preparations such as dried algae meal, annatto extract, beet powder, grape skin extract, fruit juice, paprika, caramel, carrot oil, cochineal extract, ferrous gluconate, iron oxide, turmeric) were exempted from certification, whereas all the synthetic colors were required to be retested if questions regarding their safety arose. A provisional certification was given to those in use that required further testing. Currently, there are seven certified synthetic colors (FD&C colors blue no. 1, red no. 3, red no. 40, and yellow no. 5 are permanently listed, whereas FDB blue no. 2, green no. 3, and yellow no. 6 are provisionally listed) with unlimited uses; one permanently listed color (citrus red no. 2) is used only for coloring skins of oranges at 2 ppm, and several colors including green 1, green 2, orange B, red 2, red 4, and violet 1 were delisted due to concerns of their carcinogenicity and other chronic toxic effects. A controversy linking food colors to allergies and hyperkinesis in children remains unresolved.

NANOMATERIALS IN FOOD PRODUCTS

Nanotechnology is an emerging technology that can be used in a broad array of FDA-regulated products, including medical products (to increase bioavailability of a drug), foods (to improve food packaging) and cosmetics (Magnuson et al., 2011). Materials in the nanoscale range, at least one dimension in the size range of approximately 1 nanometer (nm) to 100 nm, can exhibit different chemical or physical properties, or biological effects compared to larger-scale counterparts. In August 2015, the FDA released a policy statement indicating that it will regulate nanotechnology products under existing statutory authorities, in accordance with the specific legal standards applicable to each type of product under its jurisdiction. The FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science. To that end, the FDA's regulatory approach will have the following attributes (US FDA, 2015b):

- FDA is maintaining its product-focused, science-based regulatory policy.
- FDA's approach respects variations in legal standards for different product-classes. Nanomaterial use in food additives is looked at mainly from the safety standpoint whereas nanomaterials in drugs need to show benefits as well as acceptable safety profile.
- Where premarket review authority exists, attention to nanomaterials is being incorporated into standing procedures.
- Where statutory authority does not provide for premarket review, consultation is encouraged to reduce the risk of unintended harm to human or animal health.
- FDA will continue post-market monitoring. FDA will continue to monitor the marketplace for adverse effects from products containing nanomaterials and will take actions, as needed, to protect consumers.

- Industry remains responsible for ensuring that its products meet all applicable legal requirements, including safety standards.
- FDA will collaborate, as appropriate, with domestic and international counterparts on regulatory policy issues.
- Both for products that are not subject to premarket review and those that are, FDA will offer technical advice and guidance, as needed, to help industry meet its regulatory and statutory obligations.

DIETARY SUPPLEMENTS—NEW DIETARY INGREDIENTS

The FDA traditionally considered dietary supplements to be composed only of essential nutrients, such as vitamins, minerals, and proteins. The Nutrition Labeling and Education Act of 1990 added *herbs, or similar nutritional substances*, to the term *dietary supplement*. Through the Dietary Supplements Health and Education Act of 1994 (DSHEA), Congress expanded the meaning of the term *dietary supplements* beyond essential nutrients. DSHEA also signaled a major departure from the well-established *food* versus *drug* dichotomy that guided the FDA policy. The act reaffirmed the status of dietary supplements as foods and created a new category of foods by specifically defining dietary supplements to include such substances as ginseng, garlic, fish oils, psyllium, enzymes, glandulars, and mixtures of these. It also defines a *new dietary ingredient* (NDI) as one that meets the following definition for a *dietary supplement* and was not sold in the United States as a dietary supplement before October 15, 1994. In 2012, the FDA estimated that the number of dietary supplements on the market was 55,600 and that 5,560 new dietary supplement products come on the market each year.

According to the formal definition by DSHEA, a dietary supplement

- Is a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin a mineral, an herb or other botanical, an amino acid, a dietary substance for use by human beings to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- Is intended for ingestion in pill, capsule, tablet, or liquid form.
- Is not represented for use as a conventional food or as the sole item of a meal or diet.
- Is labeled as a *dietary supplement*.
- Includes products such as an approved new drug, certified antibiotic, or licensed biologic that was marketed as a dietary supplement or food before approval, certification, or license as a drug.

An important regulatory feature of this class of foods is that, unlike food additives, there is no requirement for premarket approval but only to provide advanced notice of new ingredient marketing at least 75 days before being introduced or delivered for introduction into interstate commerce. Under section 413(a) of the DSHEA act, a dietary supplement that contains an NDI is deemed adulterated unless it contains only dietary ingredients that "have been present in the food supply as an article used for food in a form in which the food has not been chemically altered" or "there is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe." The act authorizes the Secretary of Health and Human Services (HHS) to declare a dietary supplement as adulterated if it or one of its ingredients presents "a significant or unreasonable risk of illness or injury" when used as directed on the label, or under normal conditions of use. A dietary supplement that contains an NDI may be adulterated when there is inadequate published or manufacturer-provided information with reasonable assurance that the ingredient will not present a significant or unreasonable risk of illness or injury.

A dietary supplement is also considered adulterated if it has been prepared, packed, or held under conditions that do not meet current good manufacturing practice regulations final ruling (https://www.federalregister.gov/articles/2007/06/25/07-3039/current-good-manufacturing-practice-in-manufacturing-packaging-labeling-or-holding-operations-for). Like any other foods, it is a manufacturer's responsibility to ensure that its products are safe and properly labeled prior for marketing. The FDA has, however, the legal burden of showing that a supplement may present a health risk before it can act.

DSHEA does not specify the type or amount of evidence that must be included in an NDI notification. The newest guidance (US FDA, 2016b) recommends including in the NDI notification the following:

- A full description of the identity and composition of the NDI and the dietary supplement in which the NDI will be marketed.
- A discussion of the basis for your conclusion that the substance is an NDI.
- A description of the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling, the ordinary conditions of use of the supplement.
- An explanation of how the history of use or other evidence of safety in the notification justifies your conclusion that the dietary supplement containing the NDI will reasonably be expected to be safe.

The wording of the statute gives one a sense that the standard of safety may have been lowered for dietary supplements/NDIs compared with food additives or GRAS ingredients. The provisions not requiring endorsement either by the agency or by experts qualified by scientific training and experience to evaluate safety; placing the burden of proof on the government to demonstrate a substance is unsafe; and acceptance of *grandfathering* without stipulating consensus among experts or criteria for safety as the agency had already in place for GRAS substances; contribute to this sense (Burdock, 2000). In 2011, the FDA has issued draft guidance (Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, July 2011) related to the safety evaluation of an NDI, stating, "The NDI safety standard is different than the standard for food additives, drugs, pesticides, and other FDA-regulated products. Recommendations in guidance documents that are tailored to the safety assessment needs of other FDA-regulated products may not always be appropriate for dietary ingredients and dietary supplements," and "notifiers should use their own best judgment in compiling scientific evidence that provides a basis to conclude that the NDI that is the subject of your notification will reasonably be expected to be safe when used under the conditions recommended or suggested in the labeling of the dietary supplement described in the notification." The guidance further specifies that a change in the use of a dietary ingredient, by increasing the amount, frequency, or duration of intake compared to traditional use, triggers the classification as an NDI and, subsequently, the need for additional testing in order to complete the safety evaluation. The data needed may be derived from de novo toxicology testing, or as discussed in the section *Food Ingredients Derived from Chemically Complex Extracts*, data to evaluate safety may be available from the literature for the chemical classes that comprise the extract.

The newest FDA draft guidance (US FDA, 2016b) clarifies issues related to what is considered an NDI and what type of information the manufacturer should consider in the safety evaluation and included in the premarket notification. A decision tree approach proposed in the new draft guidance by the FDA that summarizes the testing recommendations is found in Figure 5.4.

COMPARISON OF THE REGULATORY PATHS OF FOOD INGREDIENTS

Kruger et al. (2014) summarized a comparison of regulatory paths for food additives, GRAS and Dietary supplements as shown in Table 5.5.

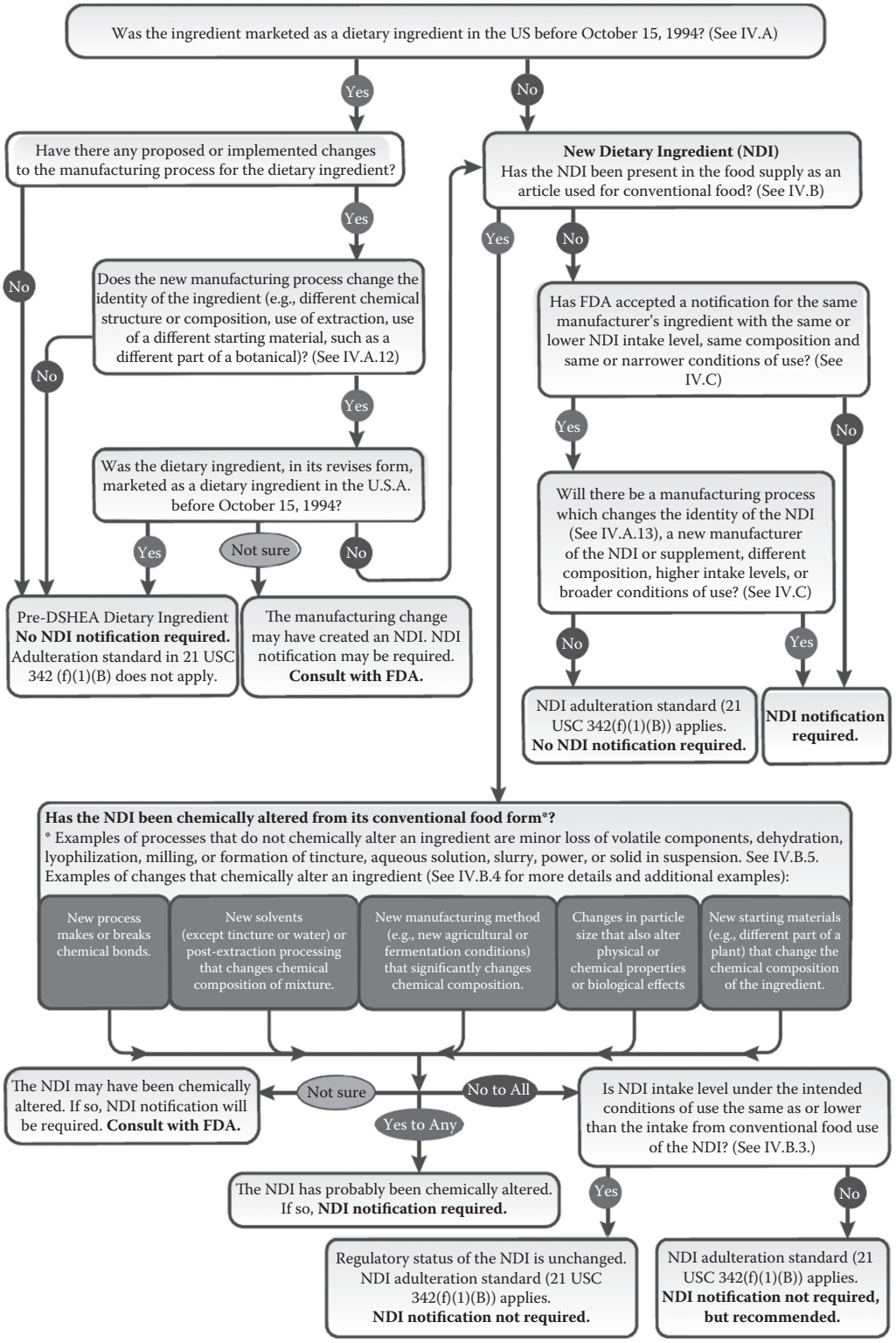

FIGURE 5.4 Decision tree approach for new toxicology testing NDI. (From US FDA, Dietary supplements: New dietary ingredient notifications and related issues: Guidance for industry: Draft guidance, August 2016.)

TABLE 5.5
Comparison of Regulatory Paths for Food Additives, GRAS Agents, and Dietary Supplements

Comparison of Regulatory Paths		
Food Additive	**GRAS**	**Dietary Supplement**
FFDC 1938	Exemption to food additives Food Additives Amendment 1958 Notification process promulgated 1997	DSHEA 1994 Draft Guidance for Industry 2011
FAP	General recognition of safety by expert panel: GRAS dossier (self-GRAS or notification)	Pre-1994: no FDA notification Post-1994: NDI notification to FDA
Information and data may be unpublished	Pivotal information and data must be published	Information and data may be unpublished
Assumes lifetime exposure	Assumes lifetime exposure	Duration and frequency of exposure dictated on label
Cannot exclude subpopulations	Cannot exclude subpopulations	Can target and exclude subpopulations on the label
EDI based on specific food uses and levels calculated using databases to derive mean and 90th percentile consumption	EDI based on specific food uses and levels calculated using databases to derive mean and 90th percentile consumption	EDI based on recommended use and levels as defined in the labeling
Reasonable certainty of no harm *specific to use/intake* Delaney clause applies	Reasonable certainty of no harm *specific to use/intake*	Reasonably expected to be safe under the conditions of use defined in the labeling
The FDA makes the determination of safety based on data provided by submitter	General recognition of safety based on publicly available data and consensus of expert panel opinion	Burden is on the submitter to establish safety for NDI under the conditions of use defined in the labeling
FDA premarket approval required	No FDA premarket approval	No FDA premarket approval
Published in 21 CFR	Record of the voluntary notification and outcome on the FDA website	Record of the mandatory premarket notification and outcome on the FDA website

Source: Kruger, C.L. et al., Food safety and food-borne toxicants, in *Hayes' Principles and Methods of Toxicology*, 6th ed., A.W. Hayes and C.L. Kruger (Eds.), CRC Press, Boca Raton, FL, pp. 621–675.

INTERNATIONAL REGULATIONS AND GLOBAL HARMONIZATION

Food additive regulation in the countries with existing procedures all agree with the general principles that food additive safety can be reasonably assured by critically designed animal studies, that the determination of safe level should be based on maximum dietary level producing no adverse effect in test animals, that the intake of the additive will be below that which could produce harmful effects in animals, that adjustment should be made to account for the safety of vulnerable populations, and that the determination of safety must be based on the judgment of scientists qualified to render such determination. There is also a universal acceptance that, for a major of new food additive, adequate animal studies are necessary to address potential mutagenicity, chronic and sub-chronic toxicity, reproductive and developmental toxicity, and carcinogenicity.

Universal international harmonization of food additive regulations, however, is currently a somewhat elusive goal because of major differences in the food use patterns, in the definitions of various additives, and in current regulations (US FDA, 1991). Magnuson et al. (2013) has summarized the regulation and safety assessment of food substances in various countries and jurisdictions. For example, the first major difference is that the only country with a GRAS list is the US. This means that compounds considered GRAS in the US may still need formal approvals in other countries. Japan has an informal GRAS approach in that they consider products that occur naturally, either in plants or through fermentation, as inherently safe. Thus, a natural compound that has undergone little testing in Japan could require investigation if it were to be exported to the US or to European countries. China considers nutrition enhancers, gum-based substances in chewing gum, and flavoring agents as direct food additives, whereas others do not. Novel foods are not specifically defined in Japan and the US. However, they are regulated as direct food additives or food contact substances in the US, whereas Japan has no authoritative statement. Many other countries have specific definitions of novel foods and respective regulations. Flavoring agents do not require premarket notification in the US and Canada and can be determined as GRAS or consulted with authorities, respectively. In Australia/New Zealand, China, the EU, Japan, and Mexico, flavoring substances are regulated and subject to approval as food additives. Indirect food additive regulations also have little to no world-wide harmonization. Japan has no definition of food contact substances and has established voluntary standards, whereas a premarket approval is required in most other countries. Enzymes and processing aids, although are undefined or varyingly defined in various countries, are uniformly regulated as either direct additives or food contact substances. Although many are in the process of studying the need for specific safety assessment regulations governing the use of nanoscale materials in foods, currently no countries have established guidelines and utilize the general principles of food additive safety.

Despite the differences mentioned earlier, attempts are being made at international harmonization. Because of similarities in the foods consumed, this has been more successful on a regional scale as exemplified by the common regulatory structures in member countries among Australia/New Zealand, Mercosur, and the EU communities. Globalization of populations and their respective food patterns necessitates greater efforts to be directed towards global harmonization of food safety regulations to ensure that consumption of foods worldwide occurs without adverse effects.

EMERGING STRATEGIES IN FOOD ADDITIVE/INGREDIENT TESTING

The National Research Council (NRC, 2007) recently recommended that safety testing of chemicals embark on a departure from the emphasis on animal model-based evaluations of apical endpoints of toxicity towards an approach that is more focused on mechanisms of toxicity (adverse outcome pathways), kinetic knowledge of internal exposure, and modeling methods. Parallel to work related to this approach were efforts to develop appropriate novel methodologies to acquire such data. These methods include: human stem cell cultures, 3D-cell cultures, organs-on-chips, models to study digestion, bioavailability, kinetics and biotransformation, and quantitative structure activity relationships (QSARs) models. In line with these developments, the possibilities to implement these new approaches in the field of foods and food ingredients are also being evaluated. Blaauboer et al. (2016) proposed a roadmap for a similar shift in the paradigm for the safety evaluation of foods and food ingredients including additives (Figure 5.5). The roadmap consists of a stepwise evaluation of the different aspects needed for a safety evaluation. These steps are designed to take into consideration factors including the possible exposure scenarios, kinetics to evaluate the internal exposure, methods to evaluate (target-specific) toxicities, mechanisms of toxicity, *in vitro/in vivo* evaluations, as well as considerations of the benefits vs. the risk of adversity. It consists of a number of blocks

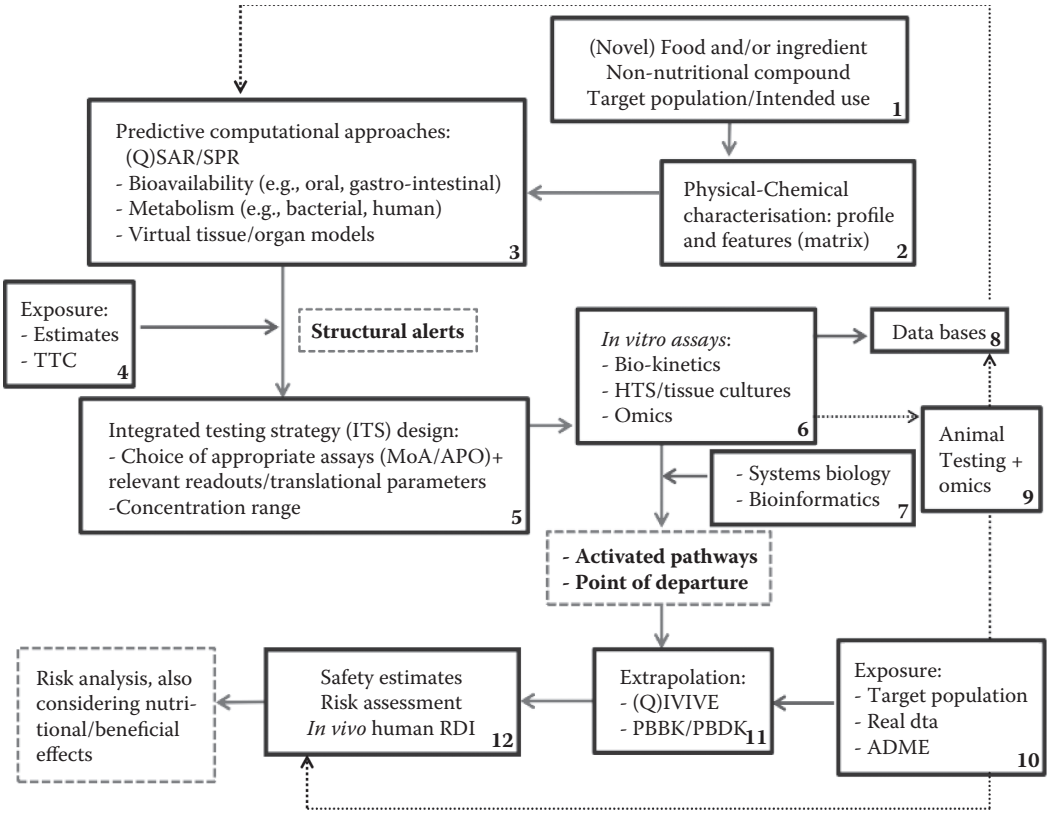

FIGURE 5.5 Evaluation roadmap for safety assessment of food and ingredients. Numbers represent the flow and the solid blocks with blue arrows the main stream. The information provided by the blocks with green arrows is related to exposure. The dotted blocks are *outcomes* of the previous blocks and the dotted lines are feedback routes and may provide additional information to (re)consider the next steps. (From Blaauboer, B.J. et al., *Food. Chem. Toxicol.*, 91, 19–35, 2016.)

that describe activities or decision steps to be taken. Each block activity aims at answering specific questions, which then may lead to activities in the following block as explained in the following (Blaauboer et al., 2016).

1. *Define the type of food*: Is it a chemically defined ingredient? A complex food ingredient? A non-nutritional compound? What is intended target population and use? This information helps to define what kind of data should be collected.
2. *Provide information on*: Physico-chemical properties (including solubility) and characterization of the material (material specification): identification of (non) nutritional compounds: changes in composition due to production process (impurities).
3. Apply computational approaches to predict for example: QSAR/QSPR (impurities); Bioaccessibility and bioavailability (behavior in the gastrointestinal [GI] tract); Metabolism (e.g., bacterial, liver); Virtual tissue/organ models for safety/efficacy assessment.
4. *Exposure assessment*: Estimation of daily exposure and apply Threshold of Toxicological Concern (TTC) concept in case of non-nutritive compounds or impurities. Consideration: if *in silico* predictions lead to one or more alerts (thus not only *approved* alerts such as genotoxicity) and/or the exposure is estimated to exceed the threshold of toxicological concern, which is often the case for foods and food ingredients, further testing is needed.

5. Design an integrated testing strategy with appropriate assays (choices should be based on the alerts, but also including considerations regarding a specific target population (pregnant women, infants) that can identify mode of action(s), determine dose response relations and measure parameters/read-outs that are translational to human population.
6. Perform *in vitro* assays (consider both nominal and measured dose concentrations), preferably medium/high throughput and based on human cells or tissues. Make use of new technologies, such as omics, imaging, etc. and include biokinetic data.
7. Apply bioinformatics tools and systems biology to integrate data and identify signatures (finger prints) and mode of actions. Consideration: can activated pathways be identified? When will they become adverse? If so, what will be the point of departure for the in vitro-in vivo extrapolation and the final safety assessment?
8. Data obtained from the *in vitro* assays should be collected and stored in databases, in such a way that the current *in silico* tools can be improved and/or new QSAR models can be build.
9. In cases where *in vitro* assays do not lead to conclusive results or do not address the relevant endpoint, or approval is needed *in vivo*, animal studies might be more considered. These tests should be designed using information from the other approaches, such as mechanistic data (e.g., from omics analyses) and can be directly used for quantitative risk assessment. These data should also be included in the databases to *validate* the in vitro assays.
10. Measure the real exposure and Absorption, Distribution, Metabolism and Excretion (ADME, or human data), specifically for target groups such as children, elderly, and obese population.
11. Combine exposure data and *in vitro* data to extrapolate from *in vitro* to *in vivo*, by using Physiologically based pharmacokinetic (PBPK) modeling, assessing how well the in vitro system mimics in vivo and considering any uncertainties.
12. Perform risk assessment, determine safety levels and human ADI, or reference daily intake (RDI) for general public and target groups.
13. Rational and mode of action supporting the beneficial or technological effects of the food or food ingredient should be considered as part of the effect spectrum, to be able to interpret potential adverse effects related to the same mode of action. This information also serves to make a risk benefit assessment with the following considerations/questions: What is the margin of safety? Is information on nutritional (beneficial) effect present? If so, is it achievable to weigh risk and benefit, considering target populations, severity of the effect (deficiency versus toxicity)?

Blaauboer et al. (2016) also examined several cases (steviol glycosides, synthetic lycopene, botanical extracts as beverages, and cetyl myristoleate complex) of food ingredients for their suitability for such evaluation and concluded that the use of the roadmap can be very helpful in reaching conclusions on their safety issues while avoiding the classical animal-based methods for such safety evaluations as much as possible. They also point out that in some instances the use of animal models may still be required for addressing specific end points such as developmental toxicity. For additional details, the reader is referred to the review by Blaauboer et al. (2016).

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6 Regulations Affecting Cosmetic and Personal Care Products

Bennett Varsho and George DeGeorge

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In the United States, the Food and Drug Administration (FDA) has statutory authority to regulate the sale of cosmetic and personal care products. Efficacy and toxicity testing is paramount to delivering useful and safe products of these types to the public. However, unlike most other areas under the FDA's purview, products in these categories do not require government approval prior to marketing. Safety assurance remains the burden of the manufacturer, but the FDA does not require submission of supporting data prior to marketing the products.

BACKGROUND

The cosmetic industry is statutorily regulated by the FDA, through the powers granted over time via the Pure Food and Drug ACT (PFDA, 1906), the Sherley Amendment (1912), Food, Drug, and Cosmetic Act (FDCA, 1938), Food and Color Amendments (1958 and 1960), and the Fair Packaging and Labeling Act (FPLA, 1967). Although the FDA does not require submission of safety data prior to a marketing approval, or dictate, sanction or even recommend safety testing strategies for cosmetic industry, there remains the possibility that the FDA could do so in the interest of public safety. Additionally, the FDA has filed lawsuits to remove dangerous products from the market and act against rogue manufacturers. These factors, along with market forces, have led to the development of a robust self-regulation of the cosmetics industry.

Industry trade organizations and the FDA have origins that trace back to the late nineteenth century, and both groups have influenced overall regulation of the industry and safety testing approaches. Figure 6.1 presents a timeline of events influencing self-regulation of the US cosmetic industry.

A product is considered a cosmetic as defined by its use. Any article that is intended to be rubbed, poured, sprinkled, sprayed on, introduced to or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness or altering the appearance is considered a cosmetic under the law.* If a

* Food, Drug, and Cosmetic Act, 1938

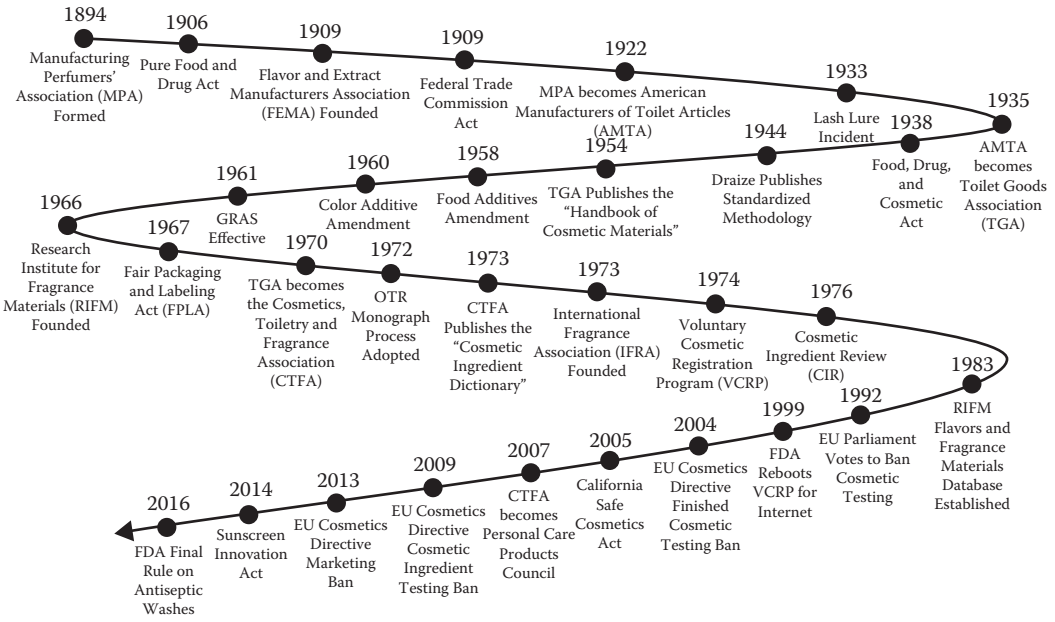

FIGURE 6.1 Events influencing self-regulation of US cosmetic industry.

TABLE 6.1
Examples of Products Regulated as Cosmetics, Drugs or Both

Regulated as a Cosmetic	Regulated as Both Cosmetic and Drug	Regulated as a Drug
Deodorant	Anti-colic infant skin moisturizer	Ketoconazole
Facial cleanser	Antidandruff shampoo	Methyl salicylate topical
Infant skin moisturizer	Antiperspirant deodorant	Tretinoin
Massage oil	Acne control facial cleanser	Silver sulfadiazine cream
Shampoo	Triclosan-fluoride toothpaste	
Skin moisturizers	Fragrant moisturizing sunburn treatment	
	Makeup with sun protection	
	Pain-relieving moisturizing massage oil	

claim to prevent, treat or cure any disease, or to affect body structure or function is made regarding a cosmetic, the product is considered a drug under the law and regulated as both. For cosmetics regulated as drugs, the FDA established an over-the-counter drug monograph process in 1972. Table 6.1 presents examples of products regulated as cosmetics, drugs or both.

THE UNITED STATES FOOD AND DRUG ADMINISTRATION

The FDA has statutory power to regulate cosmetics in the United States; however, their authority over cosmetics is much more limited than their authority over ethical drugs. Much of the FDA's authority over cosmetics devolves from the FDCA and its amendments. Under the FDCA, cosmetic manufacturers have complete responsibility to ensure that their products are safe, correctly labeled, and comply with the law. The FDA's authority over cosmetics is so limited that a description regarding cosmetic topics that lack their authority might be more useful than one for those topics over

TABLE 6.2
Scope of FDA Power over US Cosmetic Industry

Out of Scope	In Scope
Cosmetic product approval	Misbranded product
Safety testing standards	Adulterated product
Product component details	Color additives
Product registration	Harmful ingredients
Manufacturing site registration	Manufacturing inspection
Post-marketing surveillance	Recall management
Dangerous product recall	Random chemical analysis

TABLE 6.3
Adulteration and Misbranding Conditions for Cosmetic Products

Adulterated	Misbranded
It bears or contains any poisonous or deleterious substance that may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual (with an exception made for coal-tar hair dyes).	Its label does not include all required information. (An exemption may apply to cosmetics that are to be processed, labeled, or repacked at an establishment other than where they were originally processed or packed.)
It consists in whole or in part of any filthy, putrid, or decomposed substance.	Its container is so made, formed, or filled as to be misleading.
It has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.	Packaging or labeling is in violation of an applicable regulation issued pursuant to Section 3 or 4 of the Poison Prevention Packaging Act of 1970.
Its container is composed, in whole or in part, of any poisonous or deleterious substance, which may render the contents injurious to health.	Its labeling is false or misleading in any particular.
Except for coal-tar hair dyes, it is, or it bears or contains, a color additive that is unsafe within the meaning of section 721(a) of the FDCA.	It is a color additive, other than a hair dye, which does not conform to applicable regulations issued under Section 721 of the FDCA.
	The required information is not adequately prominent and conspicuous.

which they do have authority. Table 6.2 presents major areas of interest for cosmetic toxicologists in context of the scope of the FDA's authority.

Under the provisions of the 1938 FDCA, the FDA takes special interest in cosmetics that are adulterated and misbranded. The term "adulterated" is used to refer to any cosmetic product that is contaminated or otherwise contains an unsafe material. By contrast, the term "misbranded" refers not to the cosmetic product itself, but to violations of labeling and/or packaging of the product in terms of completeness and/or deception. The condition of misbranding can also be manifested under provisions of the FPLA, the Poison Control Act of 1970, and the Federal Trade Commission Act of 1914. Table 6.3 lists the specific conditions under the law for which the FDA considers a cosmetic product adulterated or misbranded.*

* Find this

If the FDA determines a product to be misbranded or adulterated may invoke its regulatory authority. Cosmetic products in violation maybe be seized by the government, and criminal actions may be initiated against the manufacturer.

COLOR ADDITIVES

Major regulation of colors in the United States began in 1906, when the US Congress passed the Pure Food and Drug Act (PFDA). This Act prohibited the use of poisonous or deleterious colors in confectionery and for the coloring of food to conceal damage or inferiority. The 1938 FDCA defines a color additive as a substance that imparts color. As an additive, under the FDCA, these agents are subject to premarket approval requirements, unless the substance is used solely for a purpose other than coloring.

Of special consideration are the coal-tar colors. There is a long history of colorants synthesized from the coal tar derivative, aniline, which numbered nearly 700 by the year 1900. Of the more than 200 color additives requiring testing in 1960, less than seven were still being tested by industry in 1982.[*] Currently, there are only about 40 organic and about 25 inorganic colorants approved for use in US cosmetics. One of the major reasons for this reduction in cosmetic colorants was the Delaney anti-cancer clause of the Kefauver–Harris Act amending the Color Additive Amendments of 1960.[†‡] This clause states that no ingredient can be safely used in a consumer product if it has been found to cause cancer in animals or man.

HARMFUL INGREDIENTS

A cosmetic manufacturer may use nearly any raw material as a cosmetic ingredient, except for the very few substances banned by the FDA. Relative to regulatory authorities in the European Union, the FDA has banned very few substances from use in cosmetics based on toxicity. Primary toxicologic effects driving the FDA's regulatory action have been carcinogenic potential, neurotoxicity, and photosensitization (photo-allergy). The agency has used different approaches in their decision making regarding banning substances. In some cases, if no better substitute can be used, a maximum concentration has been set (e.g., hexachlorophene). In other cases, the material is allowed, but only in certain applications (e.g., mercury compounds, only around the eye). Other restrictions ban materials from aerosol formulations (e.g., zirconium), are disallowed as a direct additive but are allowed in residual amounts (e.g., chloroform), and finally others are banned outright (e.g., methylene chloride). Table 6.4 presents a list of cosmetic ingredients banned in the United States, based on toxicity, as well as materials voluntarily removed from cosmetics based on industry self-regulation and/or encouragement from the FDA.[§]

While the FDA does not have power to recall cosmetic products, it can request that a manufacturer correct or remove a marketed product it considers to be in violation of the law, represent a hazard, are grossly deceptive, or are defective. The FDA will take an active role in cosmetic product recalls as specified in 21 CFR 7.[¶] The FDA will assign a classification to the product under recall, notify the public as necessary, develop a strategy for the manufacturer, monitor a recall's progress, and assure that the product is destroyed or reconditioned. Table 6.5 presents the classification scheme the FDA employs for recalled cosmetic products.

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[*] Good manufacturing practice for drug products. Federal Register, 1969; 34-6966ff
[†] Kefauver–Harris Act; Public Law No. 87-781, 1962
[‡] Rumere, M.M., Strauss, S., Kethari, A.B. Regulatory aspects of color additives. *Pharmaceutical Technology* 1992; 68–82.
[§] 21 CFR 700
[¶] 21 CFR 7

TABLE 6.4
Cosmetic Ingredients Banned Based on Toxicity in the United States

Prohibited Substance	Type	Basis for Ban	Reference	Note
Hexachlorophene	Partial	Neurotoxicity	21 CFR 250.250	Preservative not to exceed 0.1% No use on mucous membranes
Bithionol	Complete	Photosensitization	21 CFR 700.11	Antibacterial agent banned in products after March 15, 1968
Mercury compounds	Partial	Neurotoxicity, skin irritation, allergy	21 CFR 700.13	For use in eye area only Not to exceed 65 ppm
Vinyl chloride	Complete	Carcinogenic	21 CFR 700.14	Banned in aerosol products
Halogenated salicylanilides	Complete	Photosensitization	21 CFR 700.15	Banned in products introduced after December 1, 1975
Zirconium	Complete	Granuloma	21 CFR 700.16	Banned in aerosol products introduced after September 15, 1977
Chloroform	Complete	Carcinogenic	21 CFR 700.18	Residual amounts acceptable, but not as an additive
Methylene chloride	Complete	Carcinogenic	21 CFR 700.19	Fragrance material discontinued in 1978
Acetyl ethyl tetraethyl tetralin	Voluntary	Neurotoxicity	IFRA	Fragrance material discontinued in 1978
Dioxane	Voluntary	Carcinogenicity	FDA	Under FDA scrutiny since late 1970s
6-Methylcoumarin	Voluntary	Photosensitization	CIR	Fragrance material discontinued from sunscreens in 1978
Musk ambrette	Voluntary	Neurotoxicity, photosensitization	IFRA	Fragrance material discontinued in 1985
Nitrosamines	Voluntary	Carcinogenicity	FDA	FDA notice in 1979 Federal Register

TABLE 6.5
FDA Cosmetic Product Recall Classifications

Recall Classification	Description
Class I	Reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death
Class II	Reasonable probability that the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
Class III	Use of, or exposure to, a violative product is not likely to cause adverse health consequences

VOLUNTARY COSMETIC REGISTRATION PROGRAM

Since 1974, the FDA has administered the Voluntary Cosmetic Registration Program (VCRP). Cosmetic manufacturers are under no legal obligation to submit data to FDA through the VCRP.

The VCRP only applies to consumer products and not to professional-use products sold to beauty salons, spas and skin care clinics, or to cosmetic products that are not for sale (e.g., free samples and hotel-room products).

There are two surviving components from the VCRP as introduced in 1974, the registration of cosmetic establishments and the Cosmetic Product Ingredient Statement (CPIS) Program. The Product Experience Program, which was intended for cosmetic firms to submit adverse reaction reports, was discontinued based on lack of participation. Under the VCRP, only manufacturing and

packaging facilities are registered; cosmetic company locations only housing offices are not registered.* Data submitted on a CPIS include brand name, product category, ingredients listed in order of predominance, and the responsible party.†

The FDA uses the information provided voluntarily by manufacturers to evaluate marketed cosmetics. Data collected under the VCRP are also used by the Cosmetic Ingredient Review (CIR) for priority setting of their review of cosmetic ingredient safety. VCRP data may also be used by poison control centers in cases of accidental ingestion or by physicians investigating the etiology of a presented condition.

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

The FDA's Center for Food Safety and Applied Nutrition (CFSAN) administers regulations and policy governing the safety of cosmetic ingredients and finished products. CFSAN's activities include regulations, policy, and other activities dealing with proper labeling of cosmetics, regulatory and research programs to address possible health risks associated with chemical or biological contaminants, post-market surveillance and related compliance activities, industry outreach and consumer education, and international standard-setting and harmonization efforts.

In December 2016, CFSAN announced that it would make public data from the CFSAN Adverse Event Reporting System (CAERS). These data are captured from complaints made by consumers to the FDA regarding food products, dietary supplements, beverages, and cosmetic products. However, they do not contain complaints made directly to cosmetic manufacturers. Manufacturers are encouraged to share such data with the FDA, but they are under no legal compulsion to do so. Some of the aforementioned recent Congressional attempts at cosmetic law reformation would have made the submission of such data mandatory under the proposed laws.

The CAERS data are available on the CFSAN website as a CSV file for download.‡

Each event record contains a report number, the date the record was created, the date of the event leading to the complaint (if available), the role of the product (suspect or concomitant), the product name/brand name, the industry classification and associated code number, age and gender of affected person, the health outcome and coded symptoms. The raw data are not overly clean, and significant review and lumping would be required for greater confidence in any inferences drawn. For example, *100% Best Bentonite Clay, 100 Pounds*, *100% Pure Best Benzonite Clay*, *100% Pure Best Bentonite Clay*, and *100% Pure Bentonite Fine Powder* are likely the same product but have these four distinct designations. Similar, extensive data entry inconsistencies can be found in the health outcome and coded symptom fields. Nonetheless, the CAERS data are a wealth of useful information in the FDA's mission to protect public health.

A cursory examination of the CAERS public data revealed that 5,731 of 80,169 (7.1%) events reported from 2004 through 2016 were related to cosmetic products (*Cosmetics* and *Color Additive Food/Drug/Cosmetic* industry categories). Table 6.6 contains the top 10 consumer complaints by product class.

Because the FDA does not have authority to approve cosmetic products prior to market introduction, post-marketing surveillance is of paramount importance. In 2016, a case of adverse reactions to Wen hair care products was widely reported in the secular press. After the FDA had identified 127 complaints in the CAERS, an announcement was made on the FDA website on July 7, 2016 citing that the case represented "the largest number of reports ever associated with any cosmetic hair cleansing product." By December, over 1,500 complaints had been made that year. Follow-up inspections of the manufacturer's records indicate over 21,000 complaints had been received directly by the company. The Wen hair care product controversy epitomizes the value of a centralized, government-operated system for tracking adverse consumer reactions to cosmetic products.§ Figure 6.2 presents an example of a secular trend for cosmetic products easily identifiable using the FDA's CAERS.

* 21 CFR 710
† 21 CFR 720
‡ https://www.fda.gov/Food/ComplianceEnforcement/ucm494015.htm#files
§ FDA Letter to Feinstein, 2016

TABLE 6.6
Top 10 Consumer Complaints by Product Class (2004–2016)

Product Type	Complaints	Percent of Total
Vitamins/minerals/etc.	45,861	57.2
Cosmetics	5,706	7.1
Nuts/edible seed	3,324	4.1
Soft drink/water	2,527	3.2
Vegetables/vegetable products	2,463	3.1
Bakery products/dough/etc.	2,432	3.0
Fishery/seafood products	2,294	2.9
Fruit/fruit products	2,165	2.7
Milk/butter/dried milk products	1,488	1.9
Cereal preparation/breakfast food	1,222	1.5

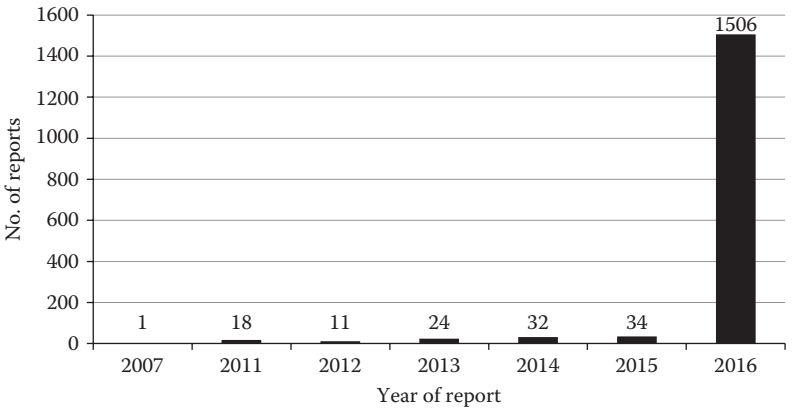

FIGURE 6.2 Consumer complaints regarding Wen hair care products in CAERS (2004–2016).

COSMETIC INGREDIENT SAFETY

In the United States, the safety of most cosmetic ingredients is determined not by the FDA or other government agency, but by the Cosmetic Ingredient Review (CIR). With the support of the FDA, the CIR was founded in 1976 by the Cosmetics, Toiletry and Fragrance Association (CTFA) (known today as the Personal Care Products Council [PCPC]) and the Consumer Federation of America (CFA). At the heart of the organization is the Expert Panel, consisting of nine (seven, minimally) publicly nominated, voting physicians and scientists. While the CIR is funded by the cosmetic industry, Expert Panel members meet the conflict-of-interest criteria like those advising the FDA. Three nonvoting liaisons (one each from the FDA, CFA, and PCPC) also serve the Expert Panel. A steering committee represents of a cross section of cosmetic industry safety stakeholders, as seen in Table 6.7, determines the general policies and direction of the CIR.

The CIR's charge is to identify those cosmetic ingredients for which there is a reasonable certainty of safety under its conditions of use.* Cosmetic ingredients are selected annually for review based on their frequency of use as reported by the industry through the FDA's VCRP, special toxicological considerations, and public commentary. Whenever appropriate, the CIR Expert Panel will consider together like ingredients. Some cosmetic ingredients are not typically evaluated by the CIR because they have other

* CIR, 2010

TABLE 6.7
Makeup of the CIR Steering Committee

Stakeholder	Representative
Personal care products council	President and CEO
Personal care products council	Executive VP for science
CIR expert panel	Panel chairperson
Cosmetic industry	Scientist
American academy of dermatologists	Dermatologist
Consumer federation of America	Consumer representative
Society of toxicology	Toxicologist

TABLE 6.8
Cosmetic Ingredients Typically Excluded from CIR

Type of Ingredient	Rationale
Fragrances	Safety evaluated by RIFM
Color additives	Reviewed under 21 CFR 71
Food additives	Reviewed under 21 CFR 171
Food flavors	GRAS Process
GRAS food ingredients	GRAS Process
OTC drug active ingredients	Reviewed under 21 CFR 300

uses that designate the primacy of other spheres of evaluation or as United States law dictates. Table 6.8 presents cosmetic ingredient types typically excluded from evaluation by the CIR.

For each cosmetic ingredient, the CIR Expert Panel considers the usage data, chemical properties, biological responses, toxicologic, clinical, and epidemiologic data. Usage data include types and numbers of products containing the ingredient and concentrations of the ingredient by usage type. Chemistry data include nomenclature, structure, details of production, and chemical and physical properties. General biological responses include absorption, distribution, metabolism, and excretion data. Toxicology data considered by the CIR can include, but are not limited to *in silico*, *in vitro*, *ex vivo*, and animal-derived toxicologic data. For a complete assessment, data on local effects (e.g., skin irritation, eye irritation, dermal sensitization) and systemic effects (e.g., acute, subchronic, chronic and developmental/reproductive toxicity and carcinogenicity) must be evaluated. Human responses, in the form of clinical trial (e.g., provocative testing) and/or epidemiologic data (e.g., case reports and controlled studies) are also included.

The CIR Expert Panel can make four basic judgments regarding safety following a cosmetic ingredient data review (Table 6.9). The findings of the CIR Expert Panel are published as monographs by the International Journal of Toxicology in CIR-specific supplemental issues.

TABLE 6.9
Four Outcomes of CIR Expert Panel Determinations

Outcome	Note
Safe ingredient	Ingredient is safe for the practices and concentrations of use
Safe ingredient w/qualification	Ingredient is safe as qualified (e.g., maximum concentration)
Unsafe ingredient	Ingredient is unsuitable based on specific adverse effects
Ingredient with insufficient data	Available data allow no conclusion regarding ingredient's safety

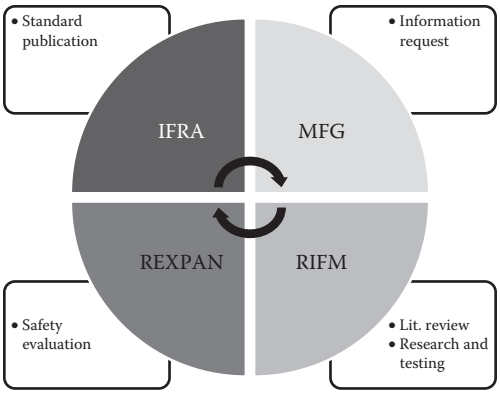

FIGURE 6.3 Fragrance product safe use risk management cycle.

As mentioned earlier, the subset of cosmetic ingredients characterized as fragrance materials is beyond the scope of the CIR's purview. The safety of fragrance materials is evaluated by another industry-funded organization, the Research Institute for Fragrance Materials (RIFM). RIFM was founded in 1966 by the industry's trade organization, the International Fragrance Association (IFRA). While both the CIR and RIFM both engage in data gathering and analysis, of the two, only RIFM has a major function in the testing of cosmetic ingredients. RIFM's research on fragrance materials is reviewed by an independent Expert Panel (REXPAN) of respiratory scientists, dermatologists, toxicologists, and environmental scientists. The resultant data are maintained in the RIFM Database, the world's largest depository of fragrance safety data, and serve as the basis for IFRA Standards. The IFRA Standards have no legal standing but have force over IFRA member companies. RIFM has evaluated over 1,000 fragrance materials, and based on those evaluations, IFRA has limited the use or banned outright the use of 100 fragrance materials by the IFRA member companies. Figure 6.3 illustrates the fragrance risk management cycle used by IFRA.[*]

Under the Fair Packaging and Labeling Act (FPLA), cosmetic ingredients must be listed on a product's label, in decreasing order of predominance. However, a fragrance need not be identified by specific ingredient, and may be simply represented as fragrance, in an effort to respect trade secrets.[†]

SAFETY TESTING OF FINISHED COSMETIC PRODUCTS

Safety testing of finished cosmetic products is not required by the FDA; however, the safety of those products is absolutely the responsibility of the manufacturer. The FDA advises manufacturers to substantiate the safety of products and their ingredients by whatever means necessary. However, the FDA states that "the safety of a product can be adequately substantiated through (a) reliance on already available toxicological test data on individual ingredients and on product formulations that are similar in composition to the particular cosmetic and (b) performance of any additional toxicological and other tests that are appropriate in light of such existing data and information."[‡]

Some (small) cosmetic manufacturers elect to perform no safety testing. In cases where the safety of a product has not been determined, the FDA mandates that the product display a message alerting the consumer. The message must state, "WARNING: The safety of this product has not been determined."[§] Any product for which the safety has not been assessed that does not bear such a warning is considered misbranded by the FDA. Startup or small manufacturers wishing to be exposed to a large audience to boost sales often first encounter requests for safety testing by the

[*] Perfumer and Flavorist, 2005
[†] FPLA
[‡] Federal Register, March 3, 1975, page 8916
[§] 21 CFR 740

television shopping networks. Presumably to protect their own brands, major television shopping networks refuse to carry cosmetic products that have not been evaluated for safety.

The cosmetic industry defines a safe cosmetic as one free from unreasonable risk or significant injury under reasonable, foreseeable conditions of use. The term "foreseeable conditions of use" has implications of common sense—it is reasonably foreseeable that something that is applied to the skin might get into the eyes; it is not reasonably foreseeable that toothpaste is applied rectally. This approach serves as a guide for safety testing of finished cosmetic and other personal care products. Table 6.10 provides potential safety testing strategies for personal care products, including many finished cosmetic types.

TABLE 6.10
Potential Safety Testing Strategies for Personal Care Products (Intended Use)

Product Type	Skin Irritation	Skin Sensitization	Eye Irritation	Mucosal Irritation	Other Concern
Acne products	✓	✓	✓		
Antiseptic wash	✓	✓	✓		Endocrine
Bath oil/beads/etc.	✓	✓	✓	✓	
Body hair bleach	✓	✓	✓		
Body paint	✓	✓	✓	✓	
Body powder	✓	✓	✓	✓	
Body soap/wash	✓	✓	✓	✓	
Body spray	✓	✓	✓	✓	
Body wipe	✓	✓	✓	✓	
Bubble bath product	✓	✓	✓	✓	
Contact lens solution	✓	✓	✓		Eye sting
Deodorant/antiperspirant	✓	✓	✓		
Denture adhesive	✓	✓	✓	✓	
Depilatory product	✓	✓	✓	✓	
Eye liner/mascara/shadow	✓	✓	✓		
Feminine care product	✓	✓	✓	✓	
Hair dye	✓	✓	✓		
Hair shampoo/rinse/etc.	✓	✓	✓		Eye sting
Hair straightener/relaxer	✓	✓	✓		
Hair styling product	✓	✓	✓		
Hand sanitizer	✓	✓	✓	✓	
Insect repellant	✓	✓	✓	✓	
Lipstick/lip balm/gloss/etc.	✓	✓	✓	✓	
Perfume	✓	✓	✓	✓	Resp. Irr./Sens.
Makeup, other	✓	✓	✓	✓	
Makeup remover	✓	✓	✓	✓	
Mouthwash	✓		✓	✓	
Nail product	✓	✓	✓		
Nasal spray	✓	✓	✓	✓	
Permanent wave/neutralizer	✓	✓	✓		
Shaving cream/gel/lotion	✓	✓	✓	✓	
Skin lightener/bleach	✓	✓	✓		
Skin cream	✓	✓	✓		
Skin salve/lotion	✓	✓	✓		
Sun tanning product	✓	✓	✓	✓	Phototoxicity
Teeth whitener	✓	✓		✓	
Toothpaste	✓	✓	✓	✓	

Some (small) cosmetic manufacturers elect to perform no safety testing. In cases where the safety of a product has not been determined, the FDA mandates that the product display a message alerting the consumer. The message must conspicuously display, "WARNING: The safety of this product has not been determined." For those products where safety testing was not performed, and a warning label is not displayed, the product is considered misbranded by the FDA. Interestingly, major television shopping networks refuse to carry cosmetic products that have not been evaluated for safety (regardless of the warning label). Frequently, small manufacturers wishing to be exposed to a large audience to boost sales will first encounter requests for safety testing by the television network.

The gold standard for safety evaluation of formulated cosmetics is a human clinical test. Large cosmetic firms sometimes operate their own clinical testing laboratories, with the attendant investigators, institutional review boards, emergency medical professionals, and so on. For manufacturers without such a facility, commercial testing laboratories provide such services for a fee. Table 6.11 presents some of the most common clinical safety studies performed for finished cosmetic products.

Although the gold standard for any finished cosmetic product safety testing is a human clinical trial, commercial clinical laboratories will require some preclinical testing prior to exposing people to novel personal care products. Through the 1980s, preclinical cosmetic testing had been typically performed using animal models; however, public distaste for using animals in this way grew through the late 1980s onward. Much of the public's disdain grew from highly imaginative and successful advertising campaigns from the People for the Ethical Treatment of Animals (PETA) and similar groups. Protests and direct actions (often illegal) rattled cosmetic firms such that many pledged to no longer use animals in finished cosmetic testing. Several firms began to allocate large amounts of resources to the development of non-animal models. The public pressure was different, and received differently in Europe, where arson and other crimes against organizations using animals in product testing were more common that in the United States. By the early 2000s, the European Commission had responded in a way that would change cosmetic testing forever.

By way of the European Commission's (EC) Cosmetic Directive, finished cosmetic products could no longer be tested using animals in the European Union (EU) after 2004. In 2009, the same Cosmetics Directive banned testing of cosmetic ingredients and combinations of ingredients. Finally, on July 11, 2013, the Cosmetic Directive was replaced with the Cosmetic Regulation (EC No. 1223/2009; legally binding to every EU member state), which brought into full effect the EU's marketing ban on cosmetic ingredients and finished products tested in animals. Since the ban was

TABLE 6.11
Common Clinical Safety Testing Studies for Personal Care Products

Clinical Trial	Endpoint	Duration	Subjects	Example Product
24-Hour patch test	Irritation	<1 week	30	Skin lotion
48-Hour cumulative irritation patch test	Irritation	~1 week	30–50	Shampoo
72-Hour cumulative irritation patch test	Irritation	~1 week	30–50	Laundry soap
96-Hour cumulative irritation patch test	Irritation	~1 week	30–50	Skin moisturizer
21-Day cumulative irritation patch test	Irritation	3 weeks	30	Perfume
Phototoxicity test	Irritation	<1 week	10	Sunscreen
Repeat-insult patch test (RIPT)	Allergy	6 weeks	25–200	Skin lotion
Photoallergy maximization test	Allergy	6 weeks	25	Sunscreen
Comedogenicity	Comedones	4–8 weeks	30–100	Facial cream
Tear-free	Tear production	<1 week	10	Shampoo
Eye instillation	Irritation	1 day	12–15	Eye drops
Eye sting	Algesia	1 day	10	Shampoo

implemented, finished cosmetic products cannot be marketed in the EU if the product has been tested using animals or if the ingredients were tested in animals. Table 6.12 presents traditional animal tests for finished cosmetics and modern non-animal replacements.

While the decision by the European Commission to ban testing of finished cosmetics products and their ingredients only has legal force in the European Union, it has had a much wider practical effect. Major cosmetic manufacturers based in countries without such bans (e.g., United States, Japan and Brazil) with an international reach, or marketing dreams thereof, must comply with the ban if they wish access to the European cosmetics market (the world's largest at $82 billion in 2015). While it was already in disfavor, the EU ban has also effectively ended finished cosmetic safety testing in animals in the United States.

TABLE 6.12
Traditional Animal Tests for Finished Cosmetics and Modern Non-Animal Replacements

Endpoint	Traditional Animal Test	Species Used	Replacement Non-Animal Test	Regulatory Guideline
Skin irritation	Draize rabbit skin irritation test	Rabbit	1. Reconstructed human epidermis skin irritation test	1. OECD TG 439
Skin sensitization	Guinea pig maximization test	Guinea pig	1. Direct peptide reactivity assay (DPRA)	1. OECD TG 442C
			2. ARE-Nrf2 luciferase test method (KeratinoSens™)	2. OECD 442D
			3. Human cell line activation test (h-CLAT)	3. OECD 442E
	Buehler assay	Guinea pig		
	Local lymph node assay	Mouse		
Eye irritation	Draize rabbit eye test	Rabbit	1. Bovine corneal opacity and permeability (BCOP)	1. OECD TG 437
			2. Reconstructed human cornea-like epithelium (RhCE) test	2. OECD TG 492
			3. Hen's egg test—Chorioallantoic membrane (HET-CAM)	3. Nonguideline
			4. Chorioallantoic membrane vascular assay (CAMVA)	4. Nonguideline
Mucosal irritation	Vaginal irritation test	Rabbit	3D Reconstructed human vaginal epithelium irritation test	Nonguideline
	Oral mucosal irritation test	Hamster	3D Reconstructed human intestinal epithelium irritation test	Nonguideline
	Penile mucosa irritation test	Rabbit	No specific model available; suggest other mucosal tissue model	Nonguideline
	Rectal mucosa irritation test	Rabbit	No specific model available; suggest other mucosal tissue model	Nonguideline
Phototoxicity	In vivo phototoxicity assay	Mouse	3T3 Neutral red uptake assay	OECD TG 432
Photosensitization	Armstrong assay	Guinea pig	Enhanced phototoxicity screening assay in reconstituted skin (EPARS)	Nonguideline
	Photo-LLNA	Mouse		
Comedogenicity	Comedogenicity assay	Rabbit		Nonguideline

For those cosmetics manufacturers seeking a global presence, China cannot be ignored. The Chinese market is the world's fastest-growing, with an estimated value of $41 billion. However, a complication arises from the intersection of the EU ban of cosmetics tested on animals and the laws of the People's Republic of China. While the EU bans safety testing of cosmetics using animals, the Chinese government mandates such testing for imported cosmetics. The arrangement is mutually exclusive: if a finished cosmetic and/or an ingredient have been tested using animals, it can't be legally sold in Europe, but it can be sold in China; conversely, if a finished cosmetic can be legally sold in Europe, because it hasn't been tested using animals, it cannot be exported to China.

This dichotomy is no small matter for cosmetic manufacturers. At least nine major cosmetics firms were found to be selling in both the Chinese and European markets in 2016. Efforts are ongoing to convince the Chinese authorities that non-animal safety tests should be accepted, however, this is presumably a decades-long strategy. A shorter-term strategy could be for cosmetics firms develop separate lines of products for the Chinese and European markets. This seemingly simple approach has at least two major drawbacks: (1) the Chinese consumers would be aware that they aren't getting the covetable products sold in Paris, London, and Milan; and (2) animal rights advocates would likely cause a public relations disaster by amplifying the fact that the cosmetics firms would have performed safety testing using animals to simply to comply with Chinese law.

A final point on the implications of the European Commission's Cosmetic Regulation that warrants mention in context of cosmetics safety testing in animals regards how cosmetic ingredients intersect with the provisions of EC No. 1907/2006, or the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). REACH is a broad government program in Europe that requires chemical manufacturers to perform safety testing on chemicals based on the production rate of the chemicals. As of 2017, most of the REACH-mandated safety testing using animals cannot be replaced with non-animal tests, be they *in silico* or *in vitro* methods.

In 2014, following implementation of European ban on testing cosmetic ingredients, some chemical manufacturers found themselves on the horns of a dilemma. Under European law, any chemical that would be used in cosmetics could undergo no testing using animals, effectively limiting its use to one sector. New chemicals to be used in cosmetics, which could potentially have other uses in food, packaging, coatings or other industries, would be pigeonholed into cosmetics only. This limitation was perceived as an innovation killer—companies developing new chemicals could be disinclined to limit their sales to a single sector or use. Furthermore, a cosmetic ingredient could be produced at such a volume as to trigger the safety testing using animals under REACH, effectively resulting in the end of a chemical allowability in the very product that made it popular.

To address the crisis, the European Commission came to an agreement with the European Chemicals Agency (ECHA) clarifying the primacy of the opposing requirements. For chemicals with a use solely in cosmetics, safety testing using animals is not permitted, except when required for environmental toxicology and occupational toxicology concerns. Chemicals with a use both in cosmetics and outside cosmetics can be tested using animals for any human health safety test, but only as a last resort. This position was developed in 2014 and was revisited in 2016. The European authorities found the 2014 position to still be sound and applicable.

PERSONAL CARE PRODUCTS REGULATED AS DRUGS

The category of consumer goods referred to as personal care products includes cosmetics, medical devices, dietary supplements, and others. Cosmetics, defined by their use, are "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body . . . for cleansing, beautifying, promoting attractiveness, or altering the appearance." Some, however, are regulated as drugs. A cosmetic product is regulated as a drug (and a cosmetic) when any therapeutic claim is made about the cosmetic, or the product is intended to alter the function or structure of the human body. These include therapeutic claims, such as anti-gingivitis

mouthwashes, anti-cavity toothpastes, and anti-acne face washes, and altering body functions, such as antiperspirants, among many others.

In an effort to address the safety of hundreds of thousands of OTC products available at the time, the Over-the-Counter (OTC) Drug Monograph Process was developed by the FDA in 1972.* The OTC Monograph Process assesses the safety and effectiveness of OTC drugs by ingredients, where the New Drug Application (NDA), assesses the safety and effectiveness of ethical drugs by product.

The OTC Monograph Process has been described by the FDA as a sort of *rule book* for marketing requirements of an OTC drug.† If a manufacturer conforms to the OTC Monograph for that indication, it can market an OTC drug product without approaching the FDA for premarketing approval.

CLAIM SUBSTANTIATION

There are two types of claims associated with personal care products: (1) cosmetic claims and (2) drug claims. Under the FDCA, the FDA has the power to fine manufacturers that misbrand personal care products. Claims are made for commercial purposes, and as such, they must be substantiated to be compliant with the Federal Trade Commission Act (FTCA). The Federal Trade Commission (FTC) has jurisdiction over advertising claims, including for personal care products. Under the FTC, advertising claims must be substantiated before disseminating. Claims to be substantiated include express and implied claims, subject to all reasonable interpretations. Consumers expect that the advertiser had a reasonable basis for making the claims. For health and safety claims, competent and reliable scientific evidence is required for substantiation.‡ The FTC expects that "tests, analyses, research, studies, or other evidence based upon the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results."§

Table 6.13 presents some common cosmetic claims made for personal care products that must be substantiated to avoid misbranding.

TABLE 6.13
Common Claim Substantiation for Personal Care Products

Skin Claims	Hair Claims	Other Claims
Acne reduction	Antidandruff	Antiperspirant
Age spots and hyperpigmentation	Anti-Frizz	Deodorant
Anti-Aging and wrinkle reduction	Bounce	Eyelash volumization
Cellulite reduction	Conditioning/detangling	Film and barrier forming effect
Collagen production	Feel	Sun protection factor (SPF)
Lip plumping	Hair counting	
Moisturization and hydration	Hair shaft diameter	
Pore size reduction	Hair thinning	
Redness reduction	Shine/oiliness	
Skin firming/elasticity	Straightening	
Skin lightening	Strengthening	
Skin toning		
Self-tanning		
Swelling, puffiness and discoloration		

* 21 CFR 330 Over-the-Counter (OTC) Human Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded
† Mahoney, K.M., Overview of the Over-the-Counter Drug Monograph Process
‡ 127 F.T.C. 580, 725
§ FTC Docket No. 9279

SPECIFIC CLASSES OF PRODUCTS

The FDA has issued regulations on broad classes of products that have special considerations, including soaps, hair dyes, sun tanning products, and antiseptic washes, among others.

Authority over the regulation of soaps in the United States is divided between the FDA and the CPSC. Any confusion by the uninitiated likely arises from imprecision of everyday language used for the not-so-simple subject of soaps. The broad, common term "soap," can be used by the public to include health-claim-free simple soaps produced from fatty-acid alkali salts, simple claim-free soaps of other composition, and body cleansers with a wide variety of claims from beautification to treating a disease condition.

Soaps, advertised solely as such and derived strictly from fats and alkali, fall under the auspices of the CPSC and do not require ingredient listing on the product label.* All other soaps and soap-like products for use on the human body are regulated by the FDA as a cosmetic, a drug, or both.

Claim-free soaps created from sources other than fat and alkali, and identified and marketed simply as soaps, are regulated by the FDA as a cosmetic. Any claims to prevent, treat or cure a disease, or to affect the function or structure of the body, such as reducing symptoms of acne and eczema, or beautifying, moisturizing, or defying age, place such a "soap" strictly under the regulatory authority of the FDA. A product's claims determine the FDA's stance on a product—medicinal claims always require drug regulation and beautification claims invoke regulation as a cosmetic, while dual claims necessitate both regulatory approaches. Regardless of the type of claim, each must be substantiated through testing. Table 6.14 provides a simple guide to the US regulatory authority over soap and soap-like products.

Like soaps, sun tanning products may be cosmetics, drugs or both. All sun tanning preparations that do not contain sunscreen ingredients are required to carry the following warning statement conspicuously on the label: "Warning: This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn."†

In 2014, the Sunscreen Innovation Act‡ was passed into law by the US Congress. The Sunscreen Innovation Act establishes a process for the submittal of data for review and approval of

TABLE 6.14
US Regulatory Authority over Soaps and Soap-Like Products

Regulated as a Soap (CPSC)	Regulated as a Cosmetic (FDA)	Regulated as a Drug (FDA)
Bulk of the nonvolatile matter in the product consists of an alkali salt of fatty acids and detergent properties arise from the alkali-fatty acid compounds.	Consists of detergents or primarily of alkali salts of fatty acids.	
Labeled, sold, and represented solely as soap.	Is intended not only for cleansing but also for other cosmetic uses.	
	Claims to make the user more attractive, by acting as a deodorant, imparting fragrance to the user, or moisturizing the skin.	
	Is intended solely for cleansing the human body.	
	Has the characteristics consumers generally associate with soap.	
	Does not consist primarily of alkali salts of fatty acids.	
	Consists of detergents, or primarily of alkali salts of fatty acids.	
	Is intended not only for cleansing but also to cure, treat, or prevent disease, or to affect the structure or any function of the human body.	

* 21 CFR 701.20
† 21 CFR 740
‡ 21 USC 9.V.I, Sunscreen Innovation Act

over-the-counter (OTC) sunscreen active ingredients. In November 2016, the FDA issued a Guidance for Industry, entitled "Nonprescription Sunscreen Drug Products—Safety and Effectiveness Data."* This guidance addresses the FDA's approach to safety and effectiveness determination of a sunscreen active ingredient combination of active ingredients, evaluated under the Sunscreen Innovation Act.

Antiseptic washes have been the subject of historical and recent rulings by the FDA. Since 1974, the FDA has been working toward establishing a monograph for OTC topical antimicrobial drug products. In September 2016, the FDA ruled that the minimum data needed to demonstrate safety for all consumer antiseptic wash's active ingredients falls into three broad categories: (1) safety data studies described in the current FDA guidance (e.g., nonclinical and human pharmacokinetic studies, developmental and reproductive toxicity studies, and carcinogenicity studies); (2) data to characterize potential hormonal effects; and (3) data to evaluate the development of bacterial resistance.† The final rule covers OTC consumer antiseptic hand and body washes, but does not cover health care antiseptics, consumer antiseptic rubs, first aid antiseptics, or antiseptics used by the food industry. Table 6.15 presents 19 consumer antiseptic wash drug products are now considered misbranded under the FDCA, based on the recent action, which goes into effect in 2017.

Rulings on benzalkonium chloride, benzethonium chloride, and chloroxylenol have been deferred. Of particular note is triclosan—a case that illustrates that a product, which was banned from external application to the body as non-Generally Recognized as Safe (GRAS) and non-Generally Recognized as Effective (GRAE), can still be used as an OTC drug in toothpaste.

Triclosan has had a number of uses in cosmetics or drugs including soaps, makeup, and toothpastes. Colgate-Palmolive added triclosan to its "Colgate Total" toothpaste in 1997. However, prior to approving the toothpaste in 1997, the FDA requested that the manufacturer substantiate safety of triclosan in an oral personal care product, resulting in the conduct and reporting of over 100 toxicity studies. Based on the submitted data, the FDA concluded triclosan was not only safe but also effective for use in toothpaste.

In 2013, an independent review of 30 studies by the Cochrane Database of Systematic Reviews concluded that toothpastes with triclosan and fluoride outperformed those with only fluoride on several counts. The triclosan-fluoride combination reduced gum inflammation by 22 percent more

TABLE 6.15
Ingredients Not Generally Recognized as Safe and Effective (GRASE) for Antiseptic Washes

Non-GRAS and Non-GRAE OTC Consumer Antiseptic Products Intended for Use with Water§

Cloflucarban	Iodophors (Iodine-containing ingredients)
Fluorosalan	Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate)
Hexachlorophene	Iodine complex (phosphate ester of alkylaryloxy polyethylene glycol)
Hexylresorcinol	Nonylphenoxypoly (ethyleneoxy) ethanoliodine
Methylbenzethonium chloride	Poloxamer-iodine complex
Phenol (greater than 1.5 percent)	Povidone-iodine 5 percent to 10 percent
Phenol (less than 1.5 percent)	Undecoylium chloride iodine complex
Secondary amyltricresols	
Sodium oxychlorosene	
Tribromsalan	
Triclocarban	
Triclosan	
Triple dye	

* Nonprescription Sunscreen Drug Products—Safety and Effectiveness Data Guidance for Industry
† Federal Register/Vol. 81, No. 172/Tuesday, September 6, 2016/Rules and Regulations
‡ *Evidence-Based Dentistry* **15**, 6–7 (2014) | doi:10.1038/sj.ebd.6400980
§ Federal Register/Vol. 81, No. 126/Thursday, June 30, 2016/Proposed Rules

and gum bleeding by 48 percent more than fluoride alone.[‡] For triclosan-containing toothpaste, the manufacturer, for now has satisfied the FDA that the benefit of triclosan in toothpaste outweighs any risks. For some critics, the decision to take triclosan out of topical products, but allow it in an oral product, is somewhat illogical.

FUTURE DIRECTIONS

Recent efforts by the US Congress to reform cosmetic regulations, while failures, portend eventual additional government regulation of the largely self-regulated cosmetics industry. Table 6.16 presents the recent Congressional efforts and their major provisions.

The Safe Cosmetics and Personal Care Products Act of 2013 (SCPCPA) was introduced by the US House of Representatives but failed to become law. The bill would have required the FDA to publish a list of all banned substances for cosmetics and conduct post-marketing testing for contaminants and pathogens. The SCPCPA would have also granted the FDA the authority to recall misbranded, adulterated, and dangerous products, and mandated manufacturers to report adverse events. Manufacturers would also have been required to advise salon workers of any health risks associated with product use. Finally, manufacturers would have been required to fund the FDA activities under the failed Act though a manufacturer registration and fee program.[*]

While the 2013 SCPCPA ultimately failed, the US Senate continued their own efforts at reforming cosmetic regulations by introducing the Personal Care Products Safety Act (PCPSA) in 2015. The PCPSA recapitulated many of the same themes of the House of Representatives offering. Under the Act, manufacturers would have had to register facilities, submit cosmetic ingredient lists,

TABLE 6.16
Features of Recent Attempts at Cosmetic Regulation Reform

Proposed New Law	Safe Cosmetics and Personal Care Products Act	Personal Care Products Safety Act	Cosmetic Modernization Amendments	Humane Cosmetics Act
Year	2013	2015	2015	2015
Introduced	H.R.1385	S.1014	H.R.4075	H.R.2858
Status	Died	Died	Died	Died
Major Provisions				
FDA recall authority	Misbranded, adulterated or dangerous	Misbranded, adulterated or dangerous		
FDA publication	Banned substances		Registrants, cosmetics and ingredients	
FDA review		5 Ingredients/year	Establish system	
FDA Post-market testing	Pathogens and contaminants			
Adverse events	Mandatory reporting	Mandatory reporting	Mandatory reporting	
Registration		Facilities	Facilities	
Ingredient list		Submit to FDA	Submit to FDA	
Inspections		Facilities/records		
Manufacturing		GMP standards	GMP standards	
Testing w/animals		Discourage use	Discourage use	Outright ban
Funding source	Industry fees	Industry fees		

[*] SCPCPA, 2013

provide details of manufacturing, and report to adverse events to the FDA. Under the PCPSA, the FDA would have been required to establish manufacturing standards, would have had power to inspect facilities and manufacturing records, would have had power to recall dangerous products or those misbranded or adulterated, would have been required to review the safety information of at least five cosmetic ingredients per year, and would have been required to encourage the use of non-animal testing methods.[*] Like the House-backed measure, the Senate-sponsored Act would have funded the FDA's activities under the act through manufacturer fees. In a letter to the Bill's sponsor, the FDA expounded their own lack of powers, commented heavily on the Bill's perceived merits, and disparaged the CIR approach to cosmetic ingredient safety assessment.[†]

While the Cosmetic Modernization Amendments (CMA) of 2015,[‡] introduced by the House, recapitulated many of the themes of the SCPCPA and the PCPSA, another House measure, the Humane Cosmetics Act of 2015,[§] was more limited in scope and addressed more directly the use of live animals in testing of cosmetic products, echoing the European Commission's decisiveness on the subject. Neither measure was passed into law, but despite the failure of the most recent congressional efforts, it seems clear that further regulation of the cosmetics industry is merely delayed, and inevitable.

[*] PCPSA, 2015
[†] FDA Letter, 2016
[‡] H.R.4075 Cosmetic Modernization Amendments
[§] H.R.2858-Humane Cosmetics Act

7 OTC Drugs and Nutraceuticals

Charles B. Spainhour

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NUTRACEUTICALS

What are nutraceuticals? Generally speaking, nutraceuticals are nutritionally or medicinally enhanced foods (Hardy, 2000; Kalra, 2003). In 1979, Stephen DeFelice, the chairman and founder of the Foundation for Innovation in Medicine (FIM, Cranford, NJ), used and defined the term nutraceuticals. According to DeFelice, nutraceuticals are defined as "food, or parts of food, that provide medical or health benefits, including the prevention and treatment of disease" (Brower, 1998; Gupta, et al., 2010; Nicoletti, 2012). Not unexpectedly, other terms were soon to follow this proposed definition. These included medical or functional food and dietary supplements. Still today, there is disagreement as to what each of these terms means. Medical foods, functional foods and dietary supplements are all specific types of nutraceuticals. Functional foods are foods, which are specifically created or supplemented to impart improved nutritional value to a food. They are freely available as OTC purchases. An example of one might be a genetically altered peanut with diminished allergenicity. Medical foods are those foods designed for consumption or enteral administration under the supervision of a physician. These foods are intended for the specific dietary management of a disease or condition and are available via prescription only (Wildman, 2001). An example might be a bottle of soda pop, which contains an antibiotic. Finally, dietary supplements are materials produced as the result of synthesis, partial synthesis, purification, isolation, or culture, which provide health benefits. These products are available as OTC products and examples might be tyrosine, carnitine, or choline (Glinsmann, 1996; Guidance for Industry, 2004, 2014).

There are many reasons for the burgeoning popularity and prevalence of nutraceuticals, especially dietary supplements. People want to control their own destiny, and this feeling applies to health also. In some cases, the use of products of this type is deeply rooted in culture. Take for instance the Japanese, they have a long history and tradition of using food for health purposes (The Japanese Standards for Herbal Medicines, 1993). Baby boomers have become disillusioned with the health care system and want more proactive control over their own health rather than merely reaction (Meyer, 1997; Brower, 1998; Chauhan, et al., 2013; Drake, et al., 2017). Place all of these feelings and philosophies against a backdrop of rising health care costs, and it is easy to appreciate at least in part why people now want to eat healthier.

The hope is that the use of nutraceuticals will provide a sufficient degree of prophylaxis to significantly decrease the costs associated with expensive visits to a physician and trips to the local pharmacy for expensive prescription drugs. A quarter of a century ago, eating healthy just meant eating a balanced diet with proper representation from each of the major food groups. Today, in all kinds of stores there are myriad new foods, which claim healthful effects. Many of these types

of products are even considered to be legitimate by insurance companies and the expense of their purchase covered in health care plans.

The availability of these products is not serendipitous. Instead, their appearance is the result of careful market research by many companies, large and small, old and new. Products associated with *healthy* eating represent a supreme opportunity, because of the attractive economic returns and an extremely lax global regulatory environment. For now, nutraceuticals, do not *require* an expensive and time-consuming process to gain marketing approval. However, with a plethora of products starting to flood the marketplace, concerns are starting to surface as to whether or not nutraceuticals, at least in some cases, are crossing the lines of demarcation between foods and drugs. This is probably best exemplified in a well-known case involving Merck, Pharmanex, the FDA and Pharmanex's product, Cholestin (Brower, 1998).

The term food generally means those commodities used for food or drink. The term drug generally refers to commodities that are intended for the diagnosis, cure, palliation, treatment, or prevention of disease. A product can be both, but applicable food and drug laws regulate food and drug products. Foods are typically considered to be safe for the average person. Drugs, alternatively, are not necessarily safe and are approved based on an acceptable benefit-to-risk ratio. This approach to regulation has become increasingly more difficult to apply, since foods are becoming progressively more visible as a result of their claimed health effects. Indeed, some foods now even contain therapeutic components (Glinsmann, 1996; Brower, 1998; Drake, et al., 2017). Such foods might be most appropriately regulated through a combination of both food and drug guidelines and laws. Such a lack of regulatory clarity and direction is consistently found not only in the US, but also Europe and Japan.

A major question to ask and answer before proceeding with the development of any potential nutraceuticals is: "Is it a food, is it a drug or is it a supplement?" (Love, 1998; Hardy, 2000; Wildman, 2001; Kalra, 2003; Gupta, et al., 2010; Nicoletti, 2012; Chauhan, et al., 2013). Keep in mind, the intended use of a proposed nutraceutical product rather than the type of ingredient in the nutraceutical product that determines the applicable review process. Drugs must be proven safe and effective for a particular indication before marketing. Food additives incur a FDA premarket review of ingredient safety. All ingredients must be Generally Recognized As Safe (GRAS) or specifically authorized as a food additive. Dietary supplements are an extremely diverse group of substances, and include, but are not limited to: amino acids, organ preparations, minerals, various extracts and concentrates, metabolites, enzymes, herbs, vitamins, botanicals, or combinations of any of these ingredients. Dietary supplements have no FDA premarket review of ingredients or finished products. They also incur no regulations concerning good manufacturing practice, identification, characterization or standardization of ingredients, efficacy, or safety.

If a nutraceutical is truly a drug, then the appropriate guidelines as set forth in Chapter 2 on human pharmaceuticals should be consulted. Global submission type developmental packages for this specific type of nutraceutical should minimally include:

1. History, origin and background information
2. Chemical structure, name, enumeration of physico-chemical properties
3. Analytical and/or bioanalytical testing methods
4. Formulation information
5. Stability test results
6. General pharmacology profile, including efficacy testing
7. ADME information: absorption, distribution, metabolism, excretion, elimination, and biological equivalence
8. Safety pharmacology profile: CNS, CV, renal, GI, and pulmonary systems
9. Toxicity profile: acute, subchronic, chronic, reproductive, carcinogenicity, mutagenicity, hypersensitivity, and antigenicity testing
10. Other specific specialty tests as appropriate
11. Clinical trial results

If the nutraceutical is a food or food additive, then appropriate regulations on foods need to be consulted (Love, 1998; Guidance for Industry, 2004, 2014) or Chapter 5 on food additives in this book. In general, a petition to be submitted for the US, Europe or Japan for this specific type of nutraceutical should minimally include the following information:

1. A complete description and characterization of the chemical and/or compositional identity of the additive. This section should also contain impurity and stability profiles and methods of analysis.
2. A complete discussion of the background and theory behind the proposed use of the additive. It is important to include an *estimated daily intake* calculation for the additive.
3. A complete description of the intended technical effect of the additive. Suitable documentation must also be provided substantiating the minimal amount of additive required to provide the intended effect.
4. Documentation of a sensitive, accurate, specific, precise, and reliable method of analysis of the additive in the food. The method should be simple and facile to perform.
5. A safety profile in support of the additive's use. This safety profile should minimally include:
   a. Safety pharmacology profile: CNS, CV, renal, GI, and pulmonary systems.
   b. Toxicology profile consistent with *concern level* as determined from *structure category* and level of dietary exposure (mg/kg per day).
   c. *Structure category* (A, B, or C) and *concern level* are determined from the Redbook II (US FDA, 1993) once the level of exposure has been calculated.

As stated previously, dietary supplements have a very broad definition, and this allows for a multitude of substances with various functional effects spanning the entire spectrum of health use. Accordingly, this only makes more complex the attempts to harmonize the regulation of development of these substances. From a global perspective the situation is even more complicated. Dietary supplements have been routinely used as part of the diet for centuries in Europe and particularly Japan and are deeply rooted in folklore and tradition. The use of these substances by the respective indigenous populations is perceived as being a right of the people and any attempt at governmental regulation would be construed as infringement on that right. Hence, there are currently no published guidelines for the development of dietary supplements in either Europe or Japan.

The culture entwining the use of dietary supplements is different in the US, so the US government attempted to address the growing use of and problems associated with these types of nutraceuticals with the passage of legislation. In 1990, the Nutritional Labeling Enforcement Act exempted medical foods from the health claim and labeling requirements applied to foods sold to healthy people. Then the Dietary Supplement Health Education Act of 1994 permitted unprecedented claims to be made about a food's or dietary supplement's ability to affect *structure and/or function* of the body. Although this latter piece of legislation was intended to create guidance in the field of integrative or alternative medical treatment research, it ended up creating significant controversy as to the necessary requirements for the approval of dietary supplement nutraceuticals regarding medical and health claims. This is because the act still did not provide any published guidelines for the development of dietary supplements in the US. The FDA should soon be providing more guidance and clarification with regard to the statement of claims for dietary supplements. Last year, the agency stated its intent to soon define the criteria for structure/function claims and describe the various means by which a dietary supplement could make or imply a disease claim prohibited under the Dietary Supplement Health Education Act. Hopefully when they appear, these new rules will provide the strongly needed clarification in the US to the currently vague differences between an unapproved and implied health claim and a legitimate structure/function claim. It is hard to say what exactly lies ahead in Europe and Japan as regarding this issue.

From a regulatory viewpoint, how a dietary supplement product is treated is determined in a large part by how it is labeled and what claims are stated on the label or while marketing the material. Therefore, it behooves one to be very scrupulous about the specific wording in a statement of claims for a potential product. Such claims and verbiage in the claims can define the entire course of performance of future safety evaluation studies. Such a course can range from the performance of no studies to a volume of work equivalent to an NDA.

With regard to the development of dietary supplements it is important to understand and appreciate the equilibrium between governmental regulation, corporate financial pressures, and ethics and liability. Governmental regulation is typically reactive and not proactive. Therefore, not unexpectedly there is a lack of formal guidance from governmental agencies with respect to the marketability of dietary supplements unless they creep into the areas of drugs or food additives. This is not surprising since historically the use of dietary supplements has not been problematic. However, the dietary supplement market has begun to explode with products. This is because businesses have finally recognized significant market opportunity in the sales of substances that have long been used by a variety of racial and ethnic groups for health purposes. The goal of business is to achieve profit margins on their products. Therefore, the cost to put products on the market is not an insignificant issue. Companies must conform to governmental regulations and guidelines while concurrently keeping a watchful eye on the costs associated with the marketing and sales of a product. Yet the issue is still more complex in that a business must also be concerned with its image and any potential liability resulting from the use or misuse of a product. From a litigious perspective, a company should be able to demonstrate *good faith* in its performance of research, development, and safety evaluation for a potential product before it is put on the market. In the development of dietary supplement nutraceuticals, it is essential to focus on the interrelationships that exist between law, profit, and liability and not just law, profit, or liability.

For the global marketing of a potentially simple, pure dietary supplement nutraceutical with no health benefit claims, the only information that is required from a regulatory perspective is a description of the product. However, one should consider a benefit-to-risk ratio in having or not having available the following additional minimal information:

1. Basic general pharmacology profile
2. Acute toxicology profile
3. Antigenicity and hypersensitivity testing
4. Other specific tests as appropriate
5. Clinical trials? (see the following)

For the global marketing of a potentially simple, pure dietary supplement nutraceutical with limited health benefit claims, the following minimal amount of information in support of a product is recommended:

1. Product description. This does not have to be detailed and does not need to include the chemical structure, composition, purity, stability analysis, or formulation information. If the product is a standardized formulation, it should be mentioned.
2. Definition of the target condition.
3. Documentation of the prevalence of the target condition.
4. Documentation of the structural or functional benefit or effect. This can assume the format of testimonials.
5. A statement of an effective dose.
6. Data or literature describing a mechanism of action or possible mechanism of action. A basic or general pharmacology profile could be included.
7. Toxicity profile: acute, subchronic, hypersensitivity, and antigenicity testing.
8. Other specific specialty tests as appropriate.
9. Clinical trials? (see the following).

For the global marketing of a potential simple or complicated, pure dietary supplement nutraceutical with far reaching health benefit claims, the minimal amount of information that should be generated during a development program would be similar, if not identical, to that previously suggested for an OTC drug or nutraceutical viewed as a drug.

For two of the paradigms described earlier for dietary supplements, clinical trials were mentioned as potential components of development packages and their potential inclusion represents a good example for the choices that need to be made in the developmental decision tree for nutraceuticals. Even though such studies are not required to corroborate claims of efficacy or safety with regard to a compound's stated structural or functional benefits, they can provide a useful function. Many companies are now considering and some even electing to perform such studies to provide stronger support to their claims and secure proprietary positions for their products.

Post-marketing surveillance takes on different forms, depending upon the type of nutraceutical. Adequate systems currently exist for foods, food additives, and drugs (Love, 1998). However, the monitoring of dietary supplements is a complex affair because there are a variety of factors that influence post-marketing safety. These factors include but are not limited to a lack of adequate scientific data on: efficacy and safety, widespread use throughout the population, chronic use, abuse, biochemical, physiological or pathological synergy, allergy, and sensitivity. This is in part a result of these products being sold via catalog sales, the internet, super markets, health food stores, and other small establishments, where no surveillance is conducted in contrast to the local pharmacy. Remember, that relative to dietary supplements, the burden of proof of significant risk of a product used according to label directions lies with the FDA before any action can be taken.

Probably the most important and lasting message to close this section with is that although there are always faster and more inexpensive ways to put products on the market, there are still only few responsible ones (Hathcock, 1993; Guidance for Industry, 2004, 2014). Following the latter path, ensures efficacy, safety and no loss of credibility (Borins, 1998; Guidance for Industry, 2004, 2014). Adjustments to this approach, made based on economy of cost, should be implemented with a full understanding of the ramifications of such action.

OTC DRUGS

United States

Over the last half-century and especially over the last 10 years, the *right* of people to diagnose and treat themselves for maladies has become prominently recognized. The demand for medicines that can be self-chosen and self-administered has become not only accepted but embraced by pharmaceutical companies. This has led to a booming market in Over-the-Counter (OTC) products and the interchangeability between prescription drugs and OTC drugs (Newton, et al., 2002; Nolan, et al., 2012; Cohen, et al., 2013; Chang, et al., 2016). The whole concept of self-treatment is still growing and developing and assuredly many changes and innovations lie ahead for the health care system, pharmaceutical companies, and regulators.

To fully understand the regulation of OTC products, a historical review is probably the best approach to take. If we go back a long time ago, a mechanism was provided for the review of new drugs with the passage of the Federal Food, Drug, and Cosmetic Act in 1938. In this piece of legislation, prescription or ethical pharmaceuticals, and OTC drugs were not differentiated from each other until the passage of the Durham-Humphrey Amendment in 1951. Product safety was the only concern and there was little to no regulatory control of OTC drugs, unless the path of litigation was pursued over issues of misrepresentation (mislabeling) or concerns for public safety (Federal Register, March 25, 1960).

With the passage of the Kefauver–Harris Amendment in 1962, all drugs were not only required to be safe, but also effective. Accordingly, the Food and Drug Administration (FDA) was forced to go back and re-evaluate all earlier submitted new drug applications. This is because all of these

drugs had been first approved with safety as the primary concern. Efficacy now needed to be confirmed. As can be easily imagined, this was a task of monumental proportions. To complete such a review process within any sort of reasonable time frame would have been impossible. Fortunately, many of the OTC products existing at the time were redundant in nature, had long histories of use in the population, were composed of similar if not identical ingredients and were associated with few adverse events when used properly and responsibly. With all of this in mind, the FDA opted to attack the review process from the perspective of reviewing and evaluating active ingredients as opposed to reviewing and evaluating individual products.

The FDA announced in January 1972, its plan of attack to re-evaluate drug products (Stringer, 1999). In this proposal, the agency stated its intent to establish a group of expert advisory review panels and requested the submission of data pertinent to OTC products that were already being sold on the market. Typically, the requests for information included but were not limited to: pharmacology data, medical data, indication data, efficacy data, toxicology data, human safety data, labeling information, and quantitative formulation data. In accordance with the stated position of an active ingredient review, a classification scheme was implemented for use by the panels. This taxonomic approach categorizes ingredients into three different groups, categories I, II, and III. The first category of active ingredients are those that are generally accepted as being safe, effective, and not misrepresented. The second category of active ingredients are those that are generally accepted as being either not safe or effective or would result in misrepresentation. The third and final category of active ingredients is for those ingredients that cannot be classified in either of the first two categories, because there is insufficient data to do so.

Individual panels were autonomous but functioned under the leadership and guidance of the FDA. They were given complete authority to review scientific data, schedule and convene open sessions, and seek consultation with other relevant scientific authorities. The mandate given to the panels was to address the efficacy and safety of each drug product using uniform and consistent standards and sound scientific principles, while adhering to the FDA' s stated position. The roles and contributions of individual ingredients in combination products were to be ascertained. Benefits and risks of products or components of products were to be defined and clarified. Finally, truthfulness of labeling was to be evaluated.

The 1972 plan also originally identified or proposed 26 different OTC drug categories, which were to be matched with a similar number of corresponding expert advisory panels. However, after additional consideration, the FDA reduced the number of panels to 17. At least part of the logic behind such a reduction was that there were several ingredients, which were used for multiple indications. In order to keep the number of expert advisory panels to a minimum and keep proper focus of discussion, the number of different use categories was defined.

Each expert advisory group conducts its review process work independently and not to any specific predetermined deadlines. However, at the conclusion of the review of each use category, the pertinent expert advisory review panel issues a report to the FDA. This report is quite extensive and complete and contains the conclusions agreed upon by the panel as well as any recommendations that the panel feels are important. The key feature of each report is what is referred to as a recommended monograph. By definition, a monograph is a book, article, and so on, written about a particular subject. The subject in this case is the use category. The monograph states the conditions under which each active ingredient is efficacious, safe and most accurately and credibly represented with regard to its use. There is a wealth of other scientific information about the use category that is included in the complete report, but which is excluded from the monograph. There are two types of such information. The first type is the identification of all active ingredients, marketing and labeling claims that could lead to a lack of safety, efficacy ,or truth in marketing and labeling. The second is the specific identification of those active and inactive ingredients and processes and wordings of advertising and labeling claims, which were excluded from discussion in the monograph, because of a lack of availability of relevant and useful data. Such a paucity of data would preclude an adequate evaluation of any considerations of efficacy or safety as well as association with the claimed indication.

After a thorough and complete review of the report submitted by the advisory review panel, the FDA then publishes a proposed monograph. The proposed monograph is then for a 60-day period open to evaluation and comment by any interested individual or group. Following this, the comments themselves are then open for review over a subsequent additional 30-day period. Finally, when all comments collected over the combined 90-day period have been evaluated and the proposed monograph modified, a draft final monograph is published. This draft final monograph is also open to a period of scrutiny and comment by any interested individual or group. At the end of this 30-day period, all questions, comments, objections, or points-raised are reviewed by the FDA for relevance and validity. Finally, an oral hearing on the draft final monograph is scheduled and convened by the commissioner. At the conclusion of this hearing, after all arguments for and against the final draft have been heard and reviewed, a final monograph is prepared and published.

Even though the monograph becomes finalized, it can still be modified via several different approaches. An individual or group may file a formal petition requesting change or amendment to the final monograph. An extreme, but not unique alternative is litigation. Finally, the commissioner may alter, at his or her own discretion, the final monograph.

Not uncommonly, drugs available by prescription only are converted to OTC availability. There are two basic ways in which this can be accomplished. In the first, the commissioner can at his or her discretion or in response to a petition make such a change in status (21 CFR 310 Subpart C). Although it is true that some drugs have had their statuses changed via this mechanism, it is no longer a commonly used method. In the second approach, new drugs can be converted from availability by prescription only to OTC availability at the request of the applicant. Such a request for a change in status is affected by either filing a New Drug Application (NDA) or a supplement to the NDA that had been previously filed. The supplemental document or new NDA must provide a compelling argument for the safety of the drug or product under consideration, especially when used without the supervision of a physician.

It is important to understand the power and significance of the final monograph. All products that differ in any way from the guidelines and standards set forth in the relevant final monograph are subject to confiscation. Furthermore, individuals associated with the actual or potential sales of such a non-compliant product are subject to legal action, up to and including federal prosecution. However, any product, which does differ from the standards and guidelines set forth in the final monograph, may still be marketed and sold as an OTC preparation by seeking approval through the filing of an NDA relevant to the difference(s) (21 CFR 330.11). Regarding this NDA *product switching* approach, it is very important to recognize that for OTC drugs, the FDA considers the relevant NDA to be a petition to amend the final monograph. Accordingly, if for whatever reason, an NDA filed in support of a switch from prescription to OTC availability is not approved, *the petition* may still be granted and marketing of the product allowed via modification of the final monograph.

NDAs filed in support of a switch from prescription to OTC availability or seeking approval of a difference from the relevant final monograph must contain certain critical information and adhere to some specific guidelines (21 CFR 330.10(a)(l2)(ii)). First, it must be shown that the product, for which approval is being sought, meets the standards of the final monograph, except as pertains to the specifically identified difference. Second, all clinical testing referenced in the NDA must be performed specifically in pursuit of an NDA. Third, the proposed product cannot have been marketed for the indication for which approval is being sought.

Inactive ingredients in OTC products must be "only suitable inactive ingredients, which are safe in the amounts administered" (Federal Register, March 29, 1974, final order 330.1 (e)). Furthermore, these inactive ingredients cannot interfere with a product's efficacy or with the procedures used and required to determine that a given product meets the claimed standards of biological potency, chemical purity, chemical concentration and identity. The inactive ingredients must not only be safe, but also serve a useful purpose (Federal Register, April 12, 1977, p. 19156).

As the market for OTC products continues to grow and develop, the FDA has responded in a supportive fashion. Historically, the agency has not considered any marketing data generated

from foreign countries. A similar lack of recognition has also been given to historical information relative to new concentrations of products already sold in the domestic market and for information concerning components that have been used for condition(s) other than those specified in an OTC monograph. However, the FDA has announced that it would consider the expansion of the list of criteria useful in performing evaluations of active ingredients in new OTC products (Federal Register, October 3, 1996, p. 51625). Under this proposal, such new criteria would potentially focus on the following: combinations of active ingredients, proposed conditions for treatment, dosage concentrations, routes of administration, and dosage forms. Furthermore, evaluations for potential new OTC products and their ingredients would include the time interval and history of use, the extent of use and the basis of use.

Europe

The *right* of people to diagnose and treat themselves for maladies has developed in Europe in parallel fashion to what has been observed in the US. European regulators depend on political support. A good example of this was in 1996, when the European Parliament and the Council of Ministers adopted resolutions that supported and recognized the importance of proper management of self-medication products and facilitated access to all EU markets (Official Journal of the European Communities, 1996). A similar view about the importance of OTC drugs has also been promulgated by the World Health Organization (WHO, 1998). What all this means is a significant growth in the OTC market in the European Community (EC). Whereas at one time, OTC products were chiefly the interest of relatively small companies, now large international companies are investing heavily in and dissecting out their OTC-related activities.

In order to facilitate economic intercourse, the EC formulated and developed a detailed program for the pharmaceutical sector (Council directive 92/26/EEC, 1992, concerning the classification for the supply of medicinal products for human use, April 30, 1992). On March 31, 1992, the EC established standards for prescription medicines and common requirements for members of the European Union (EU). In this directive, it was stated that a medicinal product is subject to medical prescription when: (1) the material presents a danger, even when used correctly, if not used under medical super-vision; (2) it is frequently used incorrectly and thereby presents a danger to humans; (3) the material contains substances that have actions or side effects that require further evaluation; and (4) its normal route of administration is parenteral. Furthermore, the directive goes on to state that medicinal products that are not classified as prescription drugs need to be classified as non-prescription drugs. One possible interpretation of this definition and position is that the EC would prefer to see products available OTC rather than available by prescription by a medical professional. Finally, it was enunciated that all medicinal products must be examined every 5 years or earlier if compelling data requiring such is presented to the regulatory authority. Where the directive fell short is in not attempting to harmonize differences between member states, but still leaving the responsibility for status inter-conversion to each member state.

A common problem in the EU concerning the conversion of a product's status from prescription availability to OTC availability is whether or not the change refers to the product or the substance. For most, but not all (UK and Germany) member states, the prescription to OTC availability change is made on a product basis. Typically, conversion from prescription to OTC status is made based on a variety of considerations. These would include: safety data available from current or prior prescription use, status conversion data from other countries and efficacy data relevant to the indication if the indication differs from that originally approved for the prescription medication. Complicating matters can be differences within the EU relative to the legal classification of various pharmaceutical ingredients. Additionally, there are often other complicating differences such as dosage, dosage form, and specified indications.

Probably the most significant development in the arena of OTC products in the EU has been the release of the European guidelines on the conversion of drugs from prescription availability

status to OTC availability (European Commission, 1998). Of not insignificant importance are the opening statements of this directive, which recognize that there are considerable differences between drug availability and drug classification between various member states in the EC and that it is very important to reduce or eliminate such differences and to harmonize positions. This guideline was intended for use by those entities seeking to make application to change the classification of a medicinal product and to facilitate harmonization within the EU. The EC chose to opt for clarification in this directive, without forcing a strict listing of products and categories on member states. Accordingly, this directive does not address differences in the rules and regulations for drug products available by OTC means. Despite its deficiencies, the directive does however, outline the criteria necessary for converting the status of a drug from prescription availability to OTC availability. Essentially, the switch of the status of a drug from prescription to OTC requires profiles of a product's safety and its potential for use and misuse. Note that no proof of efficacy is required. However, history, history of use, extent of use, and the usage pattern are other facts considered in any request for switch of status. This directive represents an important consensus between all involved authorities and is a good beginning. What remains to be determined now is how individual member states will interpret and apply the directive. Only the future can reveal this.

In conclusion, suitable guidelines are presently in place, which address the classification of prescription and nonprescription ingredients (Dechamp, 1999). However, significant differences still remain within the EU as a result of previous individual national or member state evaluations and because of political differences. Therefore, complete harmonization has not occurred and more than likely will not occur in the near future. However, the process of harmonization and current directives in place should provide a solid platform for future work and development.

Japan

The demand for increasing availability of OTC products is prominent in Japan also. Regulations and guidelines pertinent to marketing OTC drug products in Japan are covered under the registration of proprietary drugs as described in the Japanese Technical Requirements for New Drug Registration (Japanese Ministry of Health and Welfare, 1997).

Reviews for the approval of proprietary drugs are based on the nature and characteristics of proprietary products. The ingredients used must be well within a well-defined range of efficacy and safety. A similar position is taken regarding the concentrations or amounts of ingredients. Generally, drugs or products with strong action are not considered appropriate proprietary drugs. The dosage and administration of a product must be able to be competently determined and applied by the general public. Finally, allowed indications are restricted to prophylaxis, the treatment of mild disease states and the promotion of good health. Admittedly, the promotion of good health is a very vague concept most appropriately interpreted as meaning that a substance is possibly helpful and definitely not harmful. It should be obvious from this position that any conditions diagnosed and treated by physicians are not candidates for indications for proprietary drug products.

Approval standards concerning indications, ingredients, quantities, dosages, administration and effects for each therapeutic classification are prepared according to the opinions of the Central Pharmaceutical Affairs Council (CPAC). Currently, approval standards have been prepared for cold remedies, antipyretics, analgesics, antitussives, expectorants, purgatives, gastrointestinal agents, antivertigo remedies, ophthalmologics, vitamins, anthelmintics, rhinitis (nasal and oral administration), enemas, and external hemorrhoids. The authority to approve these classes of proprietary products has been delegated to the prefectural governors.

The approval review process for proprietary drugs is tied very closely with a classification scheme discriminating between new and *other* proprietary drugs.

New proprietary drugs are those drugs, which have not been approved previously as proprietary drugs. These drugs are reviewed on an individual basis by the Committee on Non-Prescription

Drugs, the Subcommittee on Non-Prescription Drugs, the Subcommittee on Chinese Medicines and Animal and Plant Origin Products and possibly others of CPAC to determine if they should be approved. Since new proprietary drugs should have indications, effects, routes of administration, and so on, identical to those approved for ethical drugs with the same ingredients, applications as ethical drugs are considered. New proprietary drugs are broken down into three different categories: (1) drugs with new active ingredients, these are referred to as *direct OTC* drugs; (2) drugs with approved ingredients used for the first time as active ingredients in proprietary drugs, these are referred to as *switch OTC* drugs; and (3) drugs whose active ingredients are already approved, but now present with different combinations of active ingredients, indications, effects, and so on.

Other drugs are those which are not new proprietary drugs. A further sub-classification is made for *other* proprietary drugs into those where approval authority has been transferred to prefectural governors and those for which the approval authority remains with the Minister of Health and Welfare (MHW). In the latter case, *other* drugs are categorized as: (4) drugs the same as new proprietary drugs, whose periods for observation for adverse reaction surveillance are over; (5) drugs with special dosage forms not in accordance with the normal approval standards; and (6) drugs that meet the approval standards for proprietary drugs, but whose approvals are issued by the MHW. Other drugs, which do not fit into the aforementioned categories (1–5) are included in this category. Proprietary drugs for which approval authority has been transferred to prefectural governors include: drugs for *tinea app.,* anthelmintics, cold treatments, drugs for rhinitis (oral and nasal administration), external hemorrhoid preparations, antipyretics, antitussives, ophthalmics, expectorants, analgesics, purgatives, vitamins and vitamin preparations, antivertigo drugs, and enemas.

The review process for proprietary drugs is, according to category: (1) a review is performed by CPAC after hearings with the MHW, (2–3) CPAC performs a review only after the Drug Organization has reviewed issues of indication, effects, dose equivalence and dose administration with those of an approved drug, (4–6) The Drug Organization conducts an equivalence review, hearings at the MHW and consultation with CPAC as necessary.

As one can easily see, the approval process for OTC products in Japan is the most complex of the three geographic and regulatory entities presented here (Japanese Ministry of Health and Welfare, 1995, 1997).

Closing Statement

Not unsurprisingly, the key to putting OTC products on the market is the ability to establish efficacy and safety. Whereas the inter-conversion of drug or product status from prescription availability to OTC availability, might appear to be simpler and even more common, the same volume of data demonstrating product safety and efficacy is ultimately required (Newton, et al., 2002; Nolan and Marmur, 2012; Cohen, et al., 2013; Chang, et al., 2016). When putting together a developmental package for a new OTC product for any regulatory agency in the world, the most responsible and successful approach is to treat a potential OTC drug or product just as one would an ethical pharmaceutical. To this end, applications should include:

1. History, origin and background information
2. Chemical structure, name, enumeration of physico-chemical properties
3. Analytical and/or bioanalytical testing methods
4. Formulation information
5. Stability test results
6. General pharmacology profile, including efficacy testing
7. ADME information: absorption, distribution, metabolism, excretion, elimination, and biological equivalence

8. Safety pharmacology profile: CNS, CV, renal, GI and pulmonary systems
9. Toxicity profile: acute, subchronic, chronic, reproductive, carcinogenicity, mutagenicity, hypersensitivity, and antigenicity testing
10. Other specific specialty tests as appropriate
11. Clinical trial results

An excellent discussion on navigating the drug development maze for human pharmaceuticals is contained in Chapter 2. The reader is urged to consult this reference to fully appreciate the requirements for developing OTC products. Lest we forget, never underestimate the importance of opening a dialogue early with the regulatory agencies of concern.

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8 Consumer Products
Nonpersonal Care Products Regulatory Review and Labeling

Robert W. Kapp and Denese A. Deeds

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INTRODUCTION

Over the past few decades, citizens in the United States have increasingly demanded a safe environment in which to reside. Haslam (2016) has provided an in-depth analysis of the psychology of the apparent expansion of concept of perceived harm that may be the underlying cause of the what citizens consider hazards in modern society. Nevertheless, access to safe medicines, foods, cosmetics, and access to products that are not hazardous is expected in today's society. For the most part, this has been a positive occurrence. In this quest for safety, citizens have demanded action from

governing officials, which, in turn, has resulted in numerous laws and regulations. Often public officials are not moved to action without public outcry resulting from catastrophic events. The poisoning and deaths of over 100 individuals (mostly children) in the 1937 Elixir Sulfanilamide Incident is a prime example. This catastrophe hastened final enactment of the Federal Food, Drug, and Cosmetic Act, which was signed into law by President Franklin Roosevelt on June 25, 1938 (FDA, 2016; Kapp, 2010). This statute today remains the basis for FDA regulation of these products. By the same token, the Environmental Protection Agency (EPA) was created in the wake of Rachel Carson's pivotal book, *Silent Spring* (Carson, 1962), about environmental pollution and how it affects bird populations and the environment overall. Further incidents, such as the lingering effects of the use of the defoliant Agent Orange in Vietnam and the Cuyahoga river fire in Cleveland, Ohio in 1969, provided impetus for the creation of the EPA. The Cuyahoga river became so polluted that it caught on fire bringing additional national attention to environmental pollution issues. In 1970, the President's Advisory Council on Executive Organization advised the formation of an Agency whose purpose was to protect the environment. Subsequently on April 22, 1970, President Nixon signed into law the National Environmental Policy Act (NEPA), which effectively created the EPA later that year (EPA, 2016).

CONSUMER PRODUCT SAFETY ACT OF 1972

Even though the FDA and EPA cover many products that could pose hazards to citizens, there remain many potentially harmful consumer products, which people come in direct contact with and are not regulated by either agency. In a 1970 fact-seeking study, which resulted in a report entitled the National Commission on Product Safety's Final Report, was issued to President Nixon and Congress. This report included surveys on product hazards, accident information systems, voluntary product standards, consumer education, the state of product safety law, the relationship between Federal law and State law, and product safety policy in other countries. The report also included proposals for general product safety legislation, ultimately resulting in the creation of a Federal Consumer Product Safety Commission (CPSC). The report revealed that not only was the American public being exposed to numerous dangerous products, but also the existing measures, such as product liability litigation, state and local regulation, industry self-regulation, and previous federal safety laws were not protecting consumers as previously was believed. Based primarily on this report, the Consumer Product Safety Act was created by Congress and signed into law also by President Nixon in 1972 as an independent Federal Regulatory Agency (15 U.S.C §§ 2051–2089). Because of the Act, the CPSC was created and made fully operational in May 1973. It was originally to be headed by three commissioners nominated by the president who are confirmed by the Senate. One of the nominees was made chairperson of the Commission; the commissioners are appointed for staggered 7-year terms. Its mission is to protect the public "against unreasonable risks of injuries associated with consumer products." These potential risks include threats from products that could cause fire, electrical, chemical or mechanical hazards or potential injuries specifically to children. Consumer products are defined as any manufactured goods (i.e., detergents, electrical appliances, clothing, cleaners, toys, cosmetics, personal care products, etc.) that are sold directly to the consumer and require no product-specific license or application to market. The Act excluded from CPSC's jurisdiction those products that are regulated by another federal agency's jurisdiction, for example, food, drugs, cosmetics, medical devices, tobacco products, firearms and ammunition, motor vehicles, pesticides, aircraft, and boats. These products may fall under the purview of agencies such as the US Food and Drug Administration (US FDA), the Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF), the US Department of Agriculture (USDA), the US Department of Transportation (USDOT), the US Environment Protection Agency (USEPA), the Federal Aviation

Administration (FAA), and/or the US Coast Guard (USCG). The CPSC is independent from any department or agency in the Federal Government. CPSC has jurisdiction over more than 15,000 kinds of consumer products used in the home, in sports and for recreation and in schools. The regulated materials are subdivided into product categories that are listed in CPSC's 2015 annual report (CPSC, 2016; Mergel, 2011):

1. Child Nursery Equipment and supplies
2. Toys
3. Sports and Recreational Activities and Equipment
4. Home Communication, Entertainment, and Hobby Equipment
5. Personal Use Items
6. Packaging and Containers for Household Products
7. Yard and Garden Equipment
8. Home Workshop Apparatus, Tools, and Attachments
9. Home and Family Maintenance Products
10. General Household Appliances
11. Space Heating, Cooling, and Ventilating Equipment
12. Housewares
13. Home Furnishings and Fixtures
14. Home Structures and Construction Materials
15. Miscellaneous Products

When CPSC became operational in May 1973, it was immediately authorized to enforce the following four existing laws (CPSC, 2016):

1. The Federal Hazardous Substances Act of 1960 (FHSA) directs the CPSC to regulate *hazardous substances* either by requiring warning labels or by banning such products when cautionary labeling proves inadequate to protect the public health and safety.
2. Flammable Fabrics Act of 1953 (FFA) authorizes CPSC to establish flammability standards to protect the public against the unreasonable risk of injury from fire.
3. The Poison Prevention Packaging Act of 1970 (PPPA) directs the CPSC to provide *special packaging* to protect children from injury or illness resulting from handling or ingesting dangerous household substances.
4. The Refrigerator Safety Act of 1956 (RSA) was enacted to deal with dozens of deaths annually resulting from children climbing into abandoned refrigerators and suffocating when the doors closed, the Act requires that refrigerator doors be easily opened from within.

Additional laws subsequently administered by CPSC include:

1. Labeling of Hazardous Art Materials Act (LHAMA) (November 18, 1988 Amendment to the FHSA)
2. The Virginia Graeme Baker Pool and Spa Safety Act (December 19, 2008)
3. The Children's Gasoline Burn Prevention Act (January 17, 2009)

CPSC does not endorse or recommend specific brands of products. Instead, CPSC provides information to consumers on the safety features of various products. In cooperation with manufacturers, CPSC also announces recalls of products that it believes pose potential risk for serious injury or death. The 1972 Consumer Product Safety Act did not provide the legal authority for CPSC to test or certify products for safety before they can be sold to consumers (Gad, 2001). The statute

permitted CPSC to require adherence to the regulations but through criminal and civil litigation after the product was on the market (CPSC, 2007). CPSC generally approaches regulation by:

- Developing voluntary standards in conjunction with industry
- Issuing and enforcing mandatory standards or banning consumer products if no feasible standard would adequately protect the public
- Recalling products or arranging for their repair
- Conducting research on potential product hazards
- Informing and educating consumers through the media, state and local governments, private organizations, and by responding to consumer inquiries

ROLE OF TOXICOLOGY

The effects of chemicals on consumer safety plays a role if the chemicals contained in each product are *bioavailable* and could result in negative effects on consumers. To meet various CPSC mandates, toxicological assessments are required. While CPSC does not require premarket clearance for a product as do FDA and EPA, if potential hazards are present, CPSC is empowered by statute to establish compliance standards in the form of packaging and/or labeling requirements. For example, explicit warning labels are required on products such as paints and cleaning agents, which contain certain toxic materials. There are also regulations limiting the sale of products containing asbestos and formaldehyde because of their chronic hazard potential. Specific test guidelines have been developed for the determination of acute toxicity for those products with inadequate safety information under the FHSA. More recently, legislation has been put forward that is specific for children's toys, which may contain lead and phthalates requiring testing to determine whether the levels of specific phthalates and lead are present at levels higher than permitted. In recent years, CPSC now encourages the use of scientifically validated alternatives to animal testing and the use of existing information, including expert opinion, prior human experience, and prior animal testing results, in the determination of hazard (CPSC, 2012). The CPSC is an active member of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and as such, supports that Committee's development and use of validated alternative test methods. ICCVAM test methods that have been approved by the CPSC for hazard determination under the FHSA with the amending of its animal testing regulations to allow alternatives to animal testing, whenever possible, under 16 CFR § 1500 (77 FR 73289) (CPSC, 2012).

Acute Effects

For each of three exposure routes (oral, dermal, and inhalation), the FHSA distinguishes two levels of acute toxicity, highly toxic and toxic, from substances that are not toxic, and therefore, LD_{50} (the amount of a substance per unit of bodyweight, given as a single dose, required to kill 50% of the test population over a period of time) or the LC_{50} (the concentration of a substance—in air or water—required to kill 50% of the test population over a period of time) do not require labeling. These terms are defined in 16 CFR § 1500.3, along with a description of the traditional method for determining the acute toxicity endpoint, the. In addition, the FSHA requires labeling of chemicals that are corrosive or irritating to eyes and skin and those that are considered strong sensitizers. Various physical hazards such as flammability also require labeling although those hazards are outside the scope of this chapter.

Oral

CPSC recommends the revised oral Up-and-Down Procedure (UDP) for determining acute oral toxicity for classification and labeling under the FHSA. The UDP is described in the Office of Prevention, Pesticides and Toxic Substances (OPPTS) Harmonized Test Guideline

870.1100 (EPA, 2002). The UDP methodology has been accepted officially by CPSC as of 2011. Further, CPSC has determined that *in vitro* basal cytotoxicity tests are appropriate for determining a starting dose for the oral LD_{50} test. The test guidelines are referenced in CPSC response to ICCVAM on the Use of In Vitro Basal Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing (CPSC, 2012).

Inhalation

Acute inhalation animal testing—OECD 403—(OECD, 2009) is recognized as the method of choice if testing for acute inhalation toxicity since no *in vitro* assays are currently recognized by CPSC in testing for inhalation toxicity.

Dermal Toxicity (LD_{50})

Acute dermal animal testing—OECD 434—(OECD, 2004) is the latest recognized as method of choice if testing for acute dermal toxicity (LD_{50}) since no *in vitro* assays are currently recognized by CPSC in testing for dermal toxicity.

Dermal Irritation

In vitro methods assessing skin irritation and corrosivity have not been assessed by CPSC. The Organization for Economic Cooperation and Development (OECD) has written guidelines outlining *in vitro* methods for determining skin irritation and corrosivity, which are described in OECD Test Guidelines 430 (OECD, 2015a) and 431 (OECD, 2016); however, no decisions are necessarily definitive using the OECD guidelines, hence the OECD guideline 402 is the current accepted methodology (OECD, 1987). The reader should note that there has been a draft update to OECD 402 dated October 2015 (OECD, 2015b); however, the status of this latest version was unknown at the time of preparation of this chapter.

Ocular Irritation

CPSC has approved a modified version of the traditional Draize rabbit eye test for ocular irritants (CPSC, 2012). Modifications to this method comprise a balanced three-part preemptive pain management strategy using topical anesthetics and/or systemic analgesics, and humane endpoints to avoid or minimize pain and distress associated with the traditional Draize method. CPSC has agreed to accept the recommendations of ICCVAM on several *in vitro* alternatives to the Draize rabbit eye test including the following:

1. The isolated chicken eye (ICE) test (use as a screening tool) (OECD, 2013a)
2. The Bovine Corneal Opacity and Permeability (BCOP) test (use as a screening tool) (OECD, 2013b)
3. Cytosensor Microphysiometer (CM) test (used with water-soluble surfactant chemicals and certain types of surfactant-containing formulations) (ICCVAM, 2011)

Sensitization

Under the CPSC regulations (16 CFR §1500.13), only designated *strong sensitizers* require specific warnings on the label. In determining if a substance or product is a *strong* sensitizer, the Commission must consider the severity of the reaction, human and animal data and conclude that there is a significant potential for hypersensitivity reaction. Currently only paraphenylenediamine and products containing it, powdered orris root and products containing it, epoxy resins systems containing in any concentration ethylenediamine, diethylenetriamine, and diglycidyl ethers of molecular weight of less than 200, formaldehyde and products containing 1% or more of formaldehyde and oil of bergamot and products containing 2% or more of oil of bergamot have been designated as strong sensitizers.

Alternative methods for testing sensitization that have been approved by the Commission include (CPSC, 2012):

1. Murine local lymph node assay (LLNA), plus LLNA method updates (OECD, 2002)
2. Reduced LLNA (OECD, 2010a)
3. Two non-radioactive versions of the LLNA (BrdU-ELISA, LLNA:DA). (OECD, 2010b)

ACUTE LABELING

Once the toxicity class(es) is established, the statute mandates the consumers be informed of these hazards through precautionary labeling. Labels must appear on the immediate containers of the hazardous product and on any outer packaging and any accompanying literature. The CPSC regulation requires the following label elements:

- The name and place of business of the manufacturer, packer, distributor, or seller
- The common or usual name or the chemical name of the hazardous substance or of each component that contributes substantially to its hazard
- Signal word "DANGER'' on substances that are extremely flammable, corrosive, or highly toxic; or the signal word "WARNING'' or "CAUTION'' on all other hazardous substances
- Affirmative statements of the principal hazard or hazards
- Precautionary measures
- First Aid Measures
- The word "POISON" for highly toxic products
- Instructions for handling and storage (when needed)
- The statement "Keep out of reach of children"

In general, the selection of the primary statements is up to the label preparer based on the hazard classification. However, certain chemicals require special mandatory label statements under the regulation (Table 8.1). These chemicals are found in 16 CFR §1500.14 and include:

Certain chemical and their mixtures that were named in the Federal Caustic Poison Act are required to have a signal word POISON rather than DANGER. These chemicals are listed in 16 CFR §1500.129 and include:

- Hydrochloric acid and any preparation containing free or chemically unneutralized hydrochloric acid (HCl) in a concentration of 10% or more
- (Sulfuric acid and any preparation containing free or chemically unneutralized sulfuric acid (H_2SO_4) in a concentration of 10% or more
- Nitric acid or any preparation containing free or chemically unneutralized nitric acid (HNO_3) in a concentration of 5% or more
- Carbolic acid (C_6H_5OH), also known as phenol, and any preparation containing carbolic acid in a concentration of 5% or more
- Oxalic acid and any preparation containing free or chemically unneutralized oxalic acid ($H_2C_2O_4$) in a concentration of 10% or more
- Any salt of oxalic acid and any preparation containing any such salt in a concentration of 10% or more
- Acetic acid or any preparation containing free or chemically unneutralized acetic acid ($HC_2H_2O_2$) in a concentration of 20% or more
- Hypochlorous acid, either free or combined, and any preparation containing the same in a concentration that will yield 10% or more by weight of available chlorine

TABLE 8.1
Examples of Substances Requiring Specific Special Labels

Chemical	Warning
Diethylene Glycol 10%	WARNING: HARMFUL IF SWALLOWED
Ethylene glycol 10%	WARNING: HARMFUL OR FATAL IF SWALLOWED
Methanol 4%	DANGER: POISON VAPOR HARMFUL. MAY BE FATAL OR CAUSE BLINDNESS IF SWALLOWED. Also "Cannot be made nonpoisonous" 
Turpentine 10%	DANGER: HARMFUL OR FATAL IF SWALLOWED
Benzene 5%	DANGER: VAPOR HARMFUL. POISON 
Toluene, Xylene 10%	VAPOR HARMFUL
Benzene, toluene, xylene, petroleum distillates 10% (VISCOSITY <100 SUS @ 100 F)	DANGER: HARMFUL OR FATAL IF SWALLOWED and Call Physician Immediately.
Charcoal	WARNING: Do Not Use for Indoor Heating or Cooking Unless Ventilation Is Provided for Exhausting Fumes to Outside. Toxic Fumes May Accumulate and Cause Death

- Potassium hydroxide and any preparation containing free or chemically unneutralized potassium hydroxide (KOH), including caustic potash and vienna paste (vienna caustic), in a concentration of 10% or more
- Sodium hydroxide and any preparation containing free or chemically unneutralized sodium hydroxide (NaOH), including caustic soda and lye in a concentration of 10% or more
- Silver nitrate, sometimes known as lunar caustic, and any preparation containing silver nitrate ($AgNO_3$) in a concentration of 5% or more
- Ammonia water and any preparation containing free or chemically uncombined ammonia (NH_3), including ammonium hydroxide and *hartshorn*, in a concentration of 5% or more

The regulations specify the placement of the required labeling on the container, the size of the font and the required conspicuousness. Details on these requirements can be found in 16 CFR §1500.121. The signal word and primary hazard statements must appear on the primary display panel in all capital letters. If all the precautionary labeling is not on the primary display panel, the front label must also contain a statement referring to the location of the additional labeling (e.g., "Read carefully other cautionary labeling on back label"). The size of font used for the warnings is dependent on the display size. The regulations define the primary display for various container types. The label preparer must calculate the size of the primary display in square inches and use the chart in 16 CFR §1500.121 to determine the minimum type size. All primary hazard statements must be the same size and boldness. Compliance with the font size is determined by measuring an upper-case letter or a lower-case letter with an ascender or descender.

Certain small containers and minor hazards are exempted from all of some of the labeling requirements. These special cases are covered in 16 CR §1500.83 and include things like some pens and markers, spot cleaners, and shoe polishes.

CHRONIC EFFECTS AND LABELING

Products that are hazardous because of chronic health effects are defined in 16 CFR §1500.3 (CPSC, 1992). They include products that are classified as carcinogens (known or probable), neurotoxicological toxicants, or developmental or reproductive toxicants. 16 CFR §1500.135 contains a summary of guidelines for assessing the risk of products that may pose a chronic health hazard to determine if they meet the definition of toxic and require labeling for those hazards. These guidelines are not mandatory. In addition to the intrinsic hazard, consideration should be given to the likelihood of exposure and resultant harm from exposure from the normal use of the product. Under the guidelines, existence of an adverse health effect means that the exposure is above the *acceptable daily intake*. Bioavailability can be considered. The guidelines can be found on the CPSC website (www.cpsc.gov) and include conclusions on acceptable risk:

- For carcinogens, the acceptable daily intake is the amount that is estimated to lead to an excess cancer risk of one in a million.
- For neurotoxins and reproductive/developmental toxicants, a safety factor approach is used.
- For human data, a safety factor of 10 is applied to the lowest NOEL (no observed effect level) and if a NOEL cannot be determined, a safety factor of 100 is applied to the LOEL (lowest observed effect level).
- For animal data, a safety factor of 100 is applied to the lowest NOEL and if a NOEL cannot be determined, a safety factor of 1000 is applied to the LOEL.

LABELING OF HAZARDOUS ART MATERIALS ACT OF 1988

In 1988, Congress passed Public Law 100–695, which amended the FHSA the Labeling of Hazardous Art Materials Act (Public Law 100–695) (*LHAMA*) and made mandatory many of the requirements of the labeling of art materials as set forth in the American Society for Testing and Materials (ASTM) standard designated D-4236 (U.S.C. 1277). It specifically included the requirement that chronically hazardous art materials must be appropriately labeled. The term art material was to include "any substance marketed or represented by the producer or repackager as suitable for use in any phase of creation of any work of visual or graphic art of any medium" (15 USC 1277[b][1]).

Over the last 5 decades, there has been an increased recognition that many chemicals have the potential to induce delayed adverse findings with long-term consequences. These effects include carcinogenicity, birth defects, and impaired reproductive effects that are cause for concern. While there have been substantial animal test data developed concerning chemicals and their ability to produce adverse effects, interpretation of the data and the application of this information to labeling for hazards requires judgment from qualified toxicologists—which is mandated in the applicable guidelines for performing label development. ASTM D-4236-94 specifically states, "an individual who through education, training, and experience has expertise in the field of toxicology, as it relates to human exposure, and is either a toxicologist or physician certified by a nationally recognized certification board" (ASTM, 2011). The two most recognized national certifications in the United States include Diplomate, American Board of Toxicology (DABT) and Fellow, Academy of Toxicological Sciences (FATS). The most common certification in the EU is the European Registered Toxicologist (ERT).

However, D-4236-94 does not specify test methods for determining whether a substance or product presents chronic health hazards (ASTM, 2011). Specifically, the producer of an art material must submit the product's formulation to a certified toxicologist to determine whether the art material has potential to produce chronic adverse health effects through customary or reasonably foreseeable use. If the toxicologist determines that the art material has this potential, appropriate

labeling must appear on the product. The producer or manufacturer of the art material must submit to the CSPC:

1. The criteria the toxicologist uses to determine whether the producer's product presents a chronic hazard
2. A list of art materials that require chronic hazard labeling

In addition to the traditional chronic effects noted earlier, D-4236-94 further specifies that permanent eye injury, specific organ damage, certain neurological and hematological effects, sensitization, and potential for excretion in human milk are to be identified as chronic effects (ASTM, 2011).

Assessment of Art Material Hazards

CPSC identifies art material in three different categories (CPSC, 2016):

1. Products that become a component of the art—for example, paint, canvas, inks, crayons, chalk, solder, brazing rods, paper, clay stone, cloth, photographic film, and so forth
2. Products that are closely and intimately associated with the creation of the final work of art—for example, brushes, brush cleaners, solvents, silk screens, mold making material, film developing chemicals, and so on
3. Tools, implements, and furniture that is used in art creation, but not part of the work of art per se—for example, drafting tables, chairs, easels, potter's wheels, hammers, chisels, picture frames, surface materials, and so on

CPSC does not consider the 3rd category to be art materials, even though they are broadly defined as such in the statute. Nevertheless, under the FHSA, manufacturers must ensure that even these peripheral items follow any FHSA labeling due to any chronic toxicity.

The CPSC published clarification of the LHAMA enforcement (February 13, 1995—60 FR 8188) and required labeling (October 13, 1995—60 FR 53266) of art and craft kits that contain materials for decorating and assembling models and art/craft items in addition to individual items.

Art materials are typically composed of mixtures of 10 or more chemicals. These complex art products rarely have any toxicity testing available. Therefore, the assessor should consider assessing the hazardous potential of these mixtures based upon the following general approach.

Concentrations of Each Component Present in the Product

The primary source of the toxic components of the art product is the manufacturer. To evaluate any toxic material, the specific concentrations/composition of all the art material components is a critical starting point. In fact, no credible evaluation can be made without the specifics of the product content. In many cases the manufacturer is reluctant to provide the product composition for fear of exposing trade secrets. This fear is entirely understandable where a specific product has been formulated for a specific purpose and there are limited similar products that can accomplish identical purposes. In most cases, a Confidentiality Agreement or Non-Disclosure Agreement is often utilized and should be employed to protect both parties from any misunderstandings of what will happen to confidential files and data. Recognizing this matter, D-4236-94 specifically notes that:

> The toxicologist shall be required to keep product formulation(s) confidential…Unless otherwise agreed in writing by the producer or repackager, no one other than the toxicologist shall have access to the formulation(s); except that the toxicologist shall furnish a patient's physician, on a confidential basis, the information necessary to diagnose or treat cases of exposure or accidental ingestion.

An example of how concentration can affect toxicity is sodium hydroxide, which is very hazardous at high concentration whereas low concentration may have a neutralizing effect on the final product

rendering it innocuous. Chemicals that are known skin sensitizers can have severely toxic effects at low concentrations. These factors must be considered by the assessor in determining the toxicity of the final product.

Toxic Properties of the Individual Components

A primary source of information on the chemical components of the art material is the manufacturer's Safety Data Sheet (SDS) on their product. Each component of the product has a SDS of the raw material, which the manufacturer has used and each has components that must be identified to make the evaluation. The manufacturer's SDS should be consistent with the SDSs of the raw materials from the suppliers. These would be good starting points for an evaluation since they should contain both acute and chronic toxicity information as well as physical and chemical properties. Information on chemical and physical properties generally available on SDSs include pH of aqueous solutions, corrosiveness, solubility, reactivity, boiling and melting points, density, and volatility. Where there is not enough information, it is incumbent on the manufacturer and/or the toxicologist to pursue the specifics of the composition of each raw material with the suppliers.

If the raw material chemicals are known and the SDS has very limited information with which one can make an evaluation, there are several accessible sources with information about chemical toxicity. The Federal Government has many databases that are freely available at on the Internet (www.toxnet.nlm.nih.gov). The individual databases include:

1. ChemIDplus (Dictionary of over 400,000 chemicals (names, synonyms, structures, and links to data sources)
2. HSDB (Hazardous Substances Data Bank. Peer-reviewed toxicology data for over 5,000 hazardous chemicals)
3. TOXLINE (Four million references to literature on biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals)
4. DART (Developmental and Reproductive Toxicology Database. References to developmental and reproductive toxicology literature)
5. IRIS (Integrated Risk Information System. Hazard identification and dose-response assessment for over 500 chemicals)
6. ITER (International Toxicity Estimates for Risk. Risk information for over 600 chemicals from authoritative groups worldwide)
7. LactMed (Drugs and Lactation Database. Drugs and other chemicals to which breastfeeding mothers may be exposed)
8. Household Products Database (Potential health effects of chemicals in more than 10,000 common household products)
9. CCRIS (Chemical Carcinogenesis Research Information System. Carcinogenicity and mutagenicity test results for over 8,000 chemicals) (n.b.—archived data—no longer updated)
10. GENE-TOX (Genetic Toxicology Data Bank. Peer-reviewed genetic toxicology test data for over 3,000 chemicals) (n.b.—archived data—no longer updated)

Another excellent source of information is Medline. This is a PubMed database that has data from 1946 from over 5,000 journals worldwide and is freely available at http://www.nlm.nih.gov/.

Other information sources include the Registry of Toxic Effects of Chemical Substances (RTECS), which originally was maintained by the National Institute for Occupational Safety and Health (NIOSH), but is now available by subscription through Symyx Technologies for a fee. The data are organized as primary irritation, mutagenic effects, reproductive effects, tumorigenic effects, acute toxicity, aquatic, in vitro toxicology, and other multiple-dose toxicity. Data such as LD_{50}, LC_{50}, TD_{Lo}, (the lowest dosage per unit of bodyweight of a substance known to have produced signs of toxicity in a particular animal species), and TC_{Lo} (lowest concentration—in air or water resulting in a toxic effect) are provided with bibliographical sources; however, the data are not evaluated or

critiqued in any way. As of 2012, the database has approximately 170,000 entries. Carcinogen data can be found at the International Agency for Research on Cancer (IARC) website (www.iarc.fr). The National Toxicology Program (NTP) provides detailed Report on Carcinogens (RoC), which is a congressionally mandated, science-based, public health document repaired for the Health and Human Service (HHS) Secretary. The 14th cumulative report was published in November 2016, and included 248 listings of agents, substances, mixtures, and exposure circumstances that are known or reasonably anticipated to cause cancer in humans.

Certainly, Google and Wikipedia can provide some data, but these are similar to RTECS and are not peer-reviewed; however, they can be helpful in locating scholarly articles. Other sources can be found in the European Chemicals Agency (ECHA) registrations (https://echa.europa.eu), eChemPortal (http://www.echemportal.org/) and Kapp, 1999.

If adequate data do not exist, one can perform an analysis of related chemicals using fee-based searches such as Derek Nexus™ and Leadscope®. ChemIDplus advanced is freely available at the US National Library of Medicine database (https://chem.nlm.nih.gov/chemidplus/). The chemical structure can be entered via ChemAxon's Marvin for JavaScript or Marvin applets and various percentages of similarity can be searched. As of November 2016, structural data are available for 326,654 records.

If these searches produce scant data and/or the exposure levels of the material are inordinately elevated, it may be necessary for the manufacturer of the product to conduct specific toxicity testing on their final product. However, if the component is present at <1%, it is very unlikely that the component would contribute significantly to the final product hazards unless it is a sensitizer. These types of agents could produce allergic reactions to some sensitized individuals and must also be evaluated by the assessor.

Considering all these data sources, the toxicologist must balance the available information and try to develop sensible and defensible recommendations for product labeling. The paucity of empirical data on many of these art products, provides many avenues for criticism of such an evaluation. To minimize the potential for a lack of accuracy, the assessor should carefully record the rationale in arriving at any conclusions about the product's inherent hazardous. For instance, the evaluation should provide calculations of how various concentrations were derived, the source of the concentrations of each component as well as literature references of toxic properties if available.

Unique Chemical/Physical Properties of the Product That Could Enhance Toxic Properties of the Total Product or Exposure Potential

Individual components of art materials possess a wide range of characteristics, which produce the properties that distinguish them as art materials. Among the components include such things as suspensions of pigments, dyes, solvents, oils, clays, plastic monomers, resin, and stabilizers. The intricacies of these types of component matrices as the assessor evaluates the toxicity of the final product mix.

Exposure Scenarios Based on Use Condition of the Product

How the user will be exposed to the art product is another critical factor in assessing toxicity. Exposure factors must consider:

1. Intended product use
2. Mode of application (heat, spraying, brushing, etc.)
3. Expected route of exposure (skin, eye, respiratory, and oral)
4. Age of user (child versus adult)
5. Percent of toxic components in the final product
6. Other components that may increase or decrease exposure to toxic elements
7. Physical properties (liquid, solid, viscosity, powder, particle size, and volatility)

For example, where there is a significant application of components that are highly volatile (e.g., paints, lacquers) there could be a release of toxic volatiles in the breathing zone of the user. Spraying

increases the exposure of toxic volatile and non-volatile components and could also present a skin or eye irritant hazard. Potential exposure of skin and eyes is high for many art materials—in particular, paints—since volatile materials and sprays enhance the levels of exposure many times. In both cases, there may be need for respiratory eye and skin protection warnings or precautionary statements.

Children's art materials present additional concerns since very young children tend to chew or eat nonfood items and lick their fingers. Many young children put non-nutritious material into their mouths at one time or another because they are naturally curious about their environment. This activity occurs in 75% of 12-month-old infants, and 15% of two-to-three-year-old children (Chatoor, 2011). Pica is the term used to described children with a pathologic bent towards putting nonfood items into their mouths, but all children do this to some extent. This activity results in oral exposure to these products. Along the same lines, the potential for dermal exposure is much higher with children since they take fewer precautions in avoiding dermal contact with the items they are using. Given the behavior of children, the toxicologist should carefully consider the greater exposure inherent in children's products and/or products that could be used by children. One must recognize the differences when labeling products for adult populations versus children. Naturally, the latter group would need a more conservative labeling warning. Where there is concern of potential exposure of children, statements should be considered that indicate when certain products should not be used by children or should be kept out of reach of children.

Assessment Overview

Overall, the assessor must closely examine more detailed technical information in supplemental documents and generally consider the following items in the evaluation of an art material (ASTM, 2011):

- Current chemical composition
- Current generally accepted, well-established scientific knowledge of the toxic potential of each component and the total formulation
- Specific physical and chemical form of the product, bioavailability, concentration, and the amount of each potentially toxic component found in the formulation
- Reasonably foreseeable uses of the product as determined by consultation with users and other individuals who are experienced in use of the material
- Potential for known synergism and antagonism
- Potentially adverse health effects of decomposition or combustion products, if known, from any reasonably foreseeable use of the hazardous art material product
- Opinions of various regulatory agencies and scientific bodies, including the International Agency for Research on Cancer and the National Cancer Institute, on the potential for chronic adverse health effects of the various components of the formulation

Labeling of Hazardous Art Materials

The labeling required must be in accordance with Section 5 of ASTM D-4236 and 16CFR 1500.14 (b)(8), which includes:

- *Signal word*: If a signal word is required for an acute hazard, the acute signal word is used. When only a chronic hazard exists, WARNING is used.
- List of potential chronic hazards (using statements substantially similar to those in 16 CFR 1500.14 (b)(8)(i)(F). Statements should be grouped in descending order of severity.
- Identification of the chronically hazardous component[s] and known decomposition products.

- Safe handling instructions substantially conforming to those listed in 16 CFR 1500.14 (b)(8)(i)(G).
- List of sensitizing components.
- Identification if a source for additional health information.
- Statement of Conformance to ASTM D-4236.

On October 9, 1992, the Commission issued a notice in the Federal Register that codified the standard as mandated by Congress. 57 FR 46626. At that time, the Commission also issued guidelines for determining when a product presents a chronic hazard, and a supplemental regulatory definition of the term ''toxic'' that explicitly includes chronic toxicity (16 CFR 1500.14[b][8]). The Standard includes requirements for placement and size of the required labeling.

CONSUMER PRODUCT SAFETY IMPROVEMENT ACT OF 2008

Consumer Reports (CRN, 2007; Kids in Danger, 2008) appropriately named 2007 the *year of the recall* with a total of 473 recalls—half of which were children's toys. This resulted in over 46 million items being recalled including lead-contaminated toy trains, collapsing cribs, and drug-tainted arts and crafts projects. There was another outcry from the public for Congress to do something. To provide the CPSC better regulatory control of the safety of products made and imported for sale into the US, the Congress passed the Consumer Product Safety Improvement Act of 2008 (CPSIA), which was signed into law by President George W. Bush on August 14, 2008 (P.L. 110–314, 2008). This law was again in response to the onerous number of safety issues primarily with children's toys. Even after the outcry, there were 563 recalls in 2008 affecting nearly 8 million toys (Consumer Reports, 2013).

Generally, CPSIA was designed to allow the CPSC to better regulate the safety of products made and imported for sale in the US. This law provided CPSC with significant new regulatory and enforcement tools as part of amending and enhancing several CPSC statutes. Under CPSIA the CPSC Office of General Counsel (CPSC-OGC) can pursue a broad range of enforcement matters with statutory and regulatory provisions, which confer a variety of mechanisms that OGC may use to support these efforts. CPSC-OGC has subpoena authority to compel the production of documents and the appearance of individuals. Additionally, civil penalty enforcement matters that are not resolved through settlement may be referred to the US Department of Justice for initiation of litigation or directly to federal court. Should OGC investigation reveal possible criminal activity, OGC can refer such matters to DOJ in accordance with agency procedures (CPSC-OGC, 2015).

The CPSIA increased the number of authorized CPSC commissioners from the original three to five. One of the major thrusts of the CPSIA legislation was to impose new testing and documentation requirements and set new limits of acceptability for lead and phthalates in toys and other children's products. CPSIA further mandated new requirements on manufacturers of clothing, shoes, personal care products, some accessories and jewelry, various home furnishings, bedding, children's toys, electronics and video games, books, educational materials, and science kits. Under CPSIA, manufacturers (including importers) are required to certify, based upon testing by an accredited third-party lab accepted by CPSC, which children's products comply with all CPSC enforced standards before the product is imported or distributed in commerce. CPSIA also called for the creation of SaferProducts.gov, a searchable database of reports of harm which became effective January 10, 2011 (16 CFR §1102). The database provides consumers with a place to turn to make more informed purchasing decisions, as well as an outlet to act when it comes to product hazards. As of August 2013, more than 15,500 reports have been posted on SaferProducts.gov (Consumer Reports, 2013).

Further, CPSIA requirements include the fact that any testing be performed on a complete unit—meaning that one product of each model or style—must be tested in its entirety. The CPSIA defines

the term "children's product" as "a consumer product designed or intended primarily for children 12 years of age or younger" (CPSIA, 2011). CPSIA specifically required that children's products:

- Comply with all applicable children's product safety rules
- Be tested for compliance by a CPSC-accepted accredited laboratory, unless subject to an exception
- Have a written Children's Product Certificate that provides evidence of the product's compliance:
  - In English
  - Provide the manufacturer's contact information
  - Date and place of manufacture
  - List of applicable rules
  - Certificate to accompany the product through distribution to the retailer
- Have permanent tracking information affixed to the product and its packaging where practicable.

The CPSIA further requires domestic manufacturers or importers of non-children's products to issue a General Certificate of Conformity (GCC). These GCC's apply to products subject to a consumer product safety rule or any similar CPSC rule, ban, standard or regulation enforced by the Commission.

CPSIA enforced standards for certain phthalates, which a manufacturer is required to test using a third-party laboratory. Section 108 of the CPSIA restricts the presence of six phthalates in children's toys and child care articles:

1. Di(2ethylhexyl) phthalate (DEHP)
2. Dibutyl phthalate (DBP)
3. Benzyl butyl phthalate (BBP)
4. Diisononyl phthalate (DINP)
5. Diisodecyl phthalate (DIDP)
6. Dinoctyl phthalate (DnOP)

These specific phthalates may not be present in concentrations >0.1% in accessible component parts of children's products (CPSC, 2014). Congress directed CPSC to seek opportunities to reduce third-party testing burdens and authorized CPSC to issue new or revised third party testing regulations if the Commission determines "that such regulations will reduce third party testing costs consistent with assuring compliance with the applicable consumer product safety rules, bans, standards, and regulations" (CPSC, 2014; TERA, 2016)

In accordance with the CPSIA, the CPSC established a Chronic Hazard Advisory Panel (CHAP) to make recommendations about whether the interim prohibitions should be made permanent and whether additional phthalates should be prohibited in children's products. CHAP recommended that the interim prohibition on Diisononyl phthalate (DINP) be made permanent and four additional phthalates (TERA, 2016):

1. Diisobutyl phthalate (DIBP)
2. Di-n-pentyl phthalate (DPENP)
3. Di-n-hexyl phthalate (DHEXP)
4. Dicyclohexyl phthalate (DCHP)

These four phthalates were to be permanently banned for use in children's toys and child care articles at concentrations >0.1%. CHAP also recommended lifting the interim ban on DnOP and DIDP. After the CHAP released its report, CPSC issued a notice of proposed rulemaking proposing

most of the CHAP's recommendations regarding prohibitions on phthalates. (79 Fed. Reg. 78324 (December 30, 2014)). Monday October 3, 2016.

Per the CPSC Fiscal Year 2015 Summary of Performance and Financial Information (CPSC, 2016), the recent strategic objectives of the CPSC include:

1. Determine the most critical consumer product hazards and issues to define the Commission's annual priorities consistent with the agency's regulatory requirements.
2. Create and strengthen partnerships with stakeholders aimed at improving product safety throughout the supply chain.
3. Collaborate with partners ranging from state and federal authorities, colleges and universities, and other stakeholders to expand the CPSC's effectiveness and reach.
4. Work towards harmonizing global consumer product standards or developing similar mechanisms to enhance product safety.
5. Promote and recognize innovation and advancements in consumer product safety.
6. Attract, retain, and collaborate with leading experts to address consumer product hazards.

CPSC has and is continuing to implement regulations based on CPSIA including the following:

- Durable Infant or Toddler Product Safety Standards
- Testing and Certification, including initial testing, periodic testing and material change testing requirements, as well as possible testing cost relief associated with component parts
- Lead limits in paint and substrates
- Phthalate limits in toys and certain child care articles
- Product Registration Cards (16 CFR §1130.1-1130.6)

IMPROVING CONSUMER PRODUCT SAFETY COMMISSION EFFECTIVENESS

CPSC continues to struggle in meting out warnings. The Consumer Product Safety Act (Section 8b) still permits the company whose product is in question to restrict and even edit what the CPSC can tell the public. If the company objects, they can send the statement back to the agency for a 5-day negotiation about what can be said. Valuable time can be expended during these times. Further delays can occur should the company take independent action. During the Samsung Galaxy Note 7 exploding batteries incident during the summer of 2016, Samsung independently issued an *unofficial recall*, which hampered the CPSC involvement since the agency is not permitted to discuss a product without giving the company a 10-day notice and actions had been initiated by the company. The Federal Aviation Authority was unable to make a definitive decision about the phones being taken on airplanes without a CPSC position on the matter over the Labor Day Weekend in September 2016 exposing many travelers to the hazards of potential exploding batteries during flights. There are internal and external efforts now underway to change current legislation to permit the CPSC to warn consumers without having to seek permission from the company in question (Novak, 2016).

As recently as October 23, 2016, GoPro began marketing *Karma*—a sophisticated drone to be used with a portable high-definition camera. A small number of the approximately 2,500 devices sold through November 5, 2016, lost power and dropped to earth, which the company states resulted in no injuries or property damage. GoPro has called for all the sold units to be returned for a full refund with some other added incentives. The product brings into focus the fact that no government agency is overseeing the safety of this type of product. CPSC spokesperson Scott Wolfson stated, "We do not have jurisdiction over drones." The Federal Aviation Administration (FAA) has jurisdiction over drone flights but does not regulate the manufacture of the devices. FAA spokesperson Alison Duquette noted that the agency does not *certify* drones during the manufacturing process the

way that it does larger aircraft. This indicates that there is some regulatory confusion about these types of products and as new technology emerges, government agencies will need to adapt quickly to oversee safety for consumers in this specific area (St. John, 2016; Kieler, 2016).

Notwithstanding these issues, CPSC continues to gather strength and has considerably more authority than in its original charter in 1972. The CPSC is headquartered in Bethesda, Maryland, with regional offices in Chicago, New York, and San Francisco with field offices in various cities across the country (16 §1000.4). CPSC also maintains a toll-free Consumer Product Safety Hotline (1-800-638-CPSC) (16 CFR §1000.3). As noted previously, CPSC also maintains a publicly searchable database of reports of unsafe products at SaferProducts.gov (16 CFR §1102).

The original budget in 1972 was $40 million with a staff of about 500 (CPSC, 1991). The sum of all operating funds available for obligation in FY 2015 was $126.0 million, a $6.4 million increase relative to FY 2014. The difference from the prior year is mostly attributable to the increase in appropriations received to fund the CPSC's import surveillance activities. The draft FY 2017 CPSC operating budget was presented in a February 2016 staff briefing. At the briefing, a budget of $130.5 million and a supporting staff of 582 was requested (CPSC FY 2017 Budget Request, 2016). These budget and staffing requests were approved on October 19, 2016 (CPSC FY 2017 Operating Plan, 2016).

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9 Agricultural Chemicals
Regulation, Risk Assessment, and Risk Management

Elliot Gordon

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INTRODUCTION

Target Audience

Toxicologists work in many different roles and areas and are involved in the hazard and risk assessment of chemicals covering a wide variety of uses and applications. In agrochemical regulatory toxicology, toxicologists work with other scientific experts, for example, ecotoxicologists, chemists, agronomists, to support the registration and safe use of pesticides, which include insecticides, herbicides, fungicides, rodenticides, bactericides, insect and plant growth regulators, insect and animal repellents, and biopesticides (derived from certain natural materials). The US Environmental Protection Agency (EPA, the Agency) notes active ingredients "prevents, destroys, repels, or mitigates a pest, or is a plant regulator, defoliant, desiccant, or nitrogen stabilizer" (US EPA, 2016a). This discipline applies sound science, conducted using confirmed methods that lead to verifiable results and conclusions. Throughout this chapter pesticide and agrichemical are used interchangeably and refer to the active ingredient. Similarly, the Agency and the EPA are used interchangeably. We are all dependent on a consistent supply of safe and nutritious food, fiber and renewable or alternative fuels. The judicious use of pesticides is one of several tools available to growers to assure this supply remains reliable.

This chapter addresses the role toxicologists play in supporting agrochemical companies with the EPA. While the generation of new data is essential for obtaining new registrations, the role of the regulatory toxicologist does not end there; incident reporting, response to Data Call-Ins, and responding to the evolving requirements of the EPA are continuously required in maintaining a registration. The data required for obtaining new registration are governed by the requirements in Code of Federal Regulations, 40 CFR part 158.

This chapter targets two audiences: (1) the *newly minted* toxicologist whose first position is in the agrochemical field, and (2) the toxicologist who has had limited experience with agrochemical registrations but is now moving into this field. Definitions are noted in Table 9.1.

TABLE 9.1
Definitions

Acronym	Note
ADME	Absorption, Distributions, Metabolism, and Excretion
a.i.	Active Ingredient
CDPR	California Department of Pesticide Regulation
CMT	Common Mechanism of Toxicity
CRO	Contract Research Organization
DAF	Dermal Absorption Factor
DART	Developmental and Reproductive Toxicology
DEEM	Dietary Exposure Evaluation Model
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency, The Agency
EUP	End-Use Product
EXAMS	Exposure Assessment
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act of 1996
IRB	Institutional Review Board
LOEL	Lowest Observed Effect Level
LOAEL	Lowest Observed Adverse Effect Level
LOC	Level of Concern
NOAEL	No-Observed-Adverse-Effect Level
MOA	Mode of Action
MOE	Margin of Exposure
MRID	Master Record Identification number
NOEL	No Observed Effect Level
OCSPP	Office of Chemical Safety and Pollution Prevention
OECD	Organization for Economic Cooperation and Development
OPP	EPA's Office of Pesticide Programs
OPPTS	EPA's Office of Prevention, Pesticides, and Toxic Substances
PHED	Pesticide Handler's Exposure Data
POD	Point of Departure
PMRA	Pest Management Regulatory Agency, Health Canada
PPE	Personal Protective Equipment
PRIA	Pesticide Registration Improvement Act
RfD	Oral Reference Dose. aRfD: acute reference dose; cRfD: chronic reference dose
TGAI	Technical Grade Active Ingredient
TSCA	Toxic Substances Control Act
UF	Uncertainty Factor
USDA	US Department of Agriculture
WHO	World Health Organization

Evolution of the Agrochemical Industry

Governments register and control the use of agricultural chemicals. In the United States, pesticide registration at both the federal and state levels is required. While some states rely predominantly on the conclusion of the EPA, others, such as the California Department of Pesticide Regulation (CDPR) are quite active in the review of agricultural chemicals and often have unique requirements or conclusions.

The Federal Insecticide Act (FIA) of 1910 was the first pesticide legislation enacted. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was passed in 1947. This addressed some shortcomings of the FIA and was under the authority of the Department of Agriculture. Rachel Carson's 1962 *Silent Spring* was a *wake up call* for the public to detrimental effects from indiscriminate use of pesticides. This concern spurred Congressional action resulting in the formation of the EPA in 1970 under president Richard Nixon's Administration. Responsibility for regulating pesticides was transferred to the EPA by the 1972 amendments to FIFRA. The EPA implements the laws enacted by Congress. In terms of agrichemicals, EPA scientists assess the risks and recommend actions regarding the registration of active ingredients (TGAI) and end-use products (EUP). EPA administrators implement these actions. The bedrock of regulatory decisions is data. Agrochemicals are thoroughly tested for potential environmental and human health effects, as well as being extensively characterized with regard to degradation in the environment and mammalian systems. Registration of a conventional pesticide requires performance of at least 100 studies performed according to harmonized test guidelines and include evaluation of effects in laboratory animals (rats, mice, dogs, rabbits) and other living organisms (e.g., plants, fish, wildlife species), metabolic and environmental degradation, and exposure estimates of the pesticide (parent compound and its metabolites) in food (raw and processed food commodities) and from product use (occupational and non-occupational, e.g., residential uses). These studies are submitted to regulatory agencies around the world for review and form the basis for the risk assessments and associated registration of pesticides. The company seeking or maintaining a pesticide registration has the responsibility to develop these data to fulfill all data requirements thus allowing the EPA to meet their regulatory standard for registering a pesticide of a *reasonable certainty of no harm* to human health or the environment.

AGROCHEMICAL REGULATION

History

Milestones in pesticide legislation are shown in Table 9.2. Since the EPA was established a number of legislative enactments have strengthened and refined its mission. Most notably is the Food Quality Protection Act (FQPA) of 1996. While this removed the Delaney Clause of 1958, which prohibited pesticide residues in processed foods, it instituted new requirements for risk assessment designed to further protect the public. An important role of the EPA is to re-evaluate all registered pesticides every 15 years.

References

Regulatory agencies promulgate guidance documents for the development and submission of data; multiple texts have been published covering both general and specific disciplines; and, peer reviewed literature continuously expands our knowledge base.

Agency Documents

The EPA along with Pest Management Regulatory Agency, Health Canada (PMRA), California Department of Pesticide Regulation (CDPR) and others publish guidance documents are accessible on the Internet. While the main focus of this chapter is the EPA, other regulatory agencies are noted, as toxicologists' activities will no doubt involve them. Web-based references may change with time (resulting in a *not found* return); therefore, the best approach to obtain the latest the EPA online references is to search using the term *US EPA* or at the regulations.gov site with the specific topic; accordingly, the reference section provides author, date, and title for most website references.

TABLE 9.2
Pesticide Related Legislation and Key Events

Year	Regulation	Comment
1910	Federal Insecticide Act	USDA concerns of fraudulent or substandard products.
1947	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA); P.L. 80-104	Extended coverage to herbicides and rodenticides. USDA registered products.
1958	Food Additives Amendment	Processed foods with residues exceeding tolerance levels were adulterated and subject to seizure similar to raw commodities. *Delaney Clause: zero tolerance for food additives found to cause cancer in animals*.
1962	*Silent Spring* published (Rachel Carson)	Risks of DDT to human health and the environment. This publication increased public awareness of the hazard potential of pesticide misuse.
1970	US Environmental Protection Agency created	
1972	Federal Environmental Pesticide Control Act; P.L. 94-140	All pesticides must be registered with EPA for general or restricted use. Pesticides cannot cause *unreasonable adverse effects on the environment*.
1973	Endangered Species Act (ESA)	Our natural heritage is of esthetic, ecological, educational, recreational, and scientific values to our nation and its people. Many native plants and animals were in danger of becoming extinct.
1975	Federal Insecticide, Fungicide, and Rodenticide Extension; P.L. 100-532	EPA to notify the Secretary of Agriculture in advance of regulatory decisions; establish a Scientific Advisory panel.
1975	EPA began to review registrations issued before August 1975, the *Rebuttable Presumption Against Registration* (*RPAR*); since renamed *Special Review.*	
1976	Toxic Substances Control Act (TSCA)	EPA regulates the manufacture, use and disposal of chemical substances; managed by the EPA Office of Pollution Prevention and Toxics (OPPT).
1987	The Clean Water Act	Protects nation's waterways from both point and non-point sources of pollution. Restrictions for runoff of agricultural chemicals.
1992	Revision of the 1974 Worker Protection Standard for Agricultural Pesticides	Modify product labels to restrict the entry of workers into pesticide–treated areas; specify the use of Personal Protective Equipment (PPE); and require notification of workers about areas treated with pesticides.
1996	Food Quality Protection Act (FQPA) of 1996; P.L. 104-170	Aggregate and Cumulative risk assessments; extra safety factors for infants and children; endocrine disruption data required.
2003	Pesticide Registration Improvement Act (PRIA) of 2003; P.L. 108-199	Establishes fees and time-lines associated with pesticide registration.
2012	PRIA Extension Act (PRIA 3); P.L. 112-177	Update of PRIA fees.

Note: The current FIFRA statue was established by P.L. 92-516, which completely replaced (by amendment) the original 1947 legislation.

Literature

Peer reviewed papers represent advances in toxicology. Apart from the routine publications you get from their professional societies (e.g., ACT, SOT, SETAC, ISRTP)*. Internet searches are the main means of finding new references.

Handling of References

The substantial number of references is both a blessing and a challenge. The blessing is that one has resources to formulate scientific position papers, waivers and scientific debates with the Agency; the challenge is how to organize them in a manner that supports their efficient identification and use. Consider reference managers that are commercially available (Wikipedia, 2016). Depending on the software, once references are entered, along with keywords, abstracts and, in many cases, the document itself, are ready for relevant citations purposes. This chapter was written with the aid of EndNote (Thomson Reuters, 2016).

Industry Groups

Industry groups share scientific and regulatory information, scientific position papers and evaluate data. These are shared and discussed with the Agency. Toward that end, consider participating in industry committees, task forces or consortia. CropLife America represents agrichemical companies; American Chemistry Council includes many of the same companies but focuses on the chemical industry; and, Industry Task Forces are formed to respond to specific regulatory toxicology issues. Task forces have addressed occupational exposure, endocrine disruption, epidemiology and more. These task forces are highly beneficial not only for the established regulatory toxicologist but provide a specialized forum for the new toxicologist.

Regulators

It is important to build a relationship of professionalism and trust with the Agency. In order to accomplish that, it is of the utmost importance to prepare and submit *sound* science-based arguments with adequate data to the Agency prior to the meeting. Come to meetings prepared and be able to calmly and professionally discuss the science as well as understand the regulatory policies to which the Agency must adhere. It is important to cultivate good relations with government scientists and Agency Product Managers. While the US Food and Drug Administration (FDA) requires all communications to go through the Product Manager, individual EPA scientists are often amenable to direct communications. Apart from the obvious benefits, they are valuable source of information and clarifications/insight of issues that may be stumbling blocks in obtaining registrations. As mentioned earlier, in many instances the Agency is restricted by regulatory policies that include not only the legislative mandates, but also litigation pressure from environmental groups as well as juggle with court ordered deadlines. Toxicologists work with contacts in regulatory agencies to solve issues, build trust and show that they can be a resource for regulators as much as regulators are for toxicologists. When antagonism is replaced by cooperation, benefits are more likely to occur.

AGROCHEMICAL RISK ASSESSMENT

The steps for risk assessment are Hazard Identification; Dose Response Assessment; Exposure Assessment; and Risk Characterization (NAS, 1983). Agencies have elaborated on this paradigm (CDPR, 2013; Health Canada, 2013; US EPA, 2015a, 2015d, 2016d).

* ACT: American College of Toxicology; SOT: Society of Toxicology; SETAC: Society of Environmental Toxicology and Chemistry; ISRTP: International Society of Regulatory Toxicology & Pharmacology.

There is an important distinction between hazard-based regulations and risk-based regulations. While hazard-based risk assessments are promoted in the European Union (Nordlander, Simon, & Pearson, 2010) and Brazil (Paumgartten, 2012), the EPA relies on risk-based assessments (US EPA, 2015a). Risk-based assessments rely on the formula:

$$\text{Risk} = \text{Hazard} \times \text{Exposure}$$

In the absence of exposure, there is no risk. Relying exclusively on hazard, in regulating chemicals does not serve society (Zaruk, 2015). Removing crop protection chemicals based on hazard alone, when adequate means to control exposure exist, makes successful farming more difficult.

Hazard Identification

40 CFR Part 158 identifies EPA data requirements for registration of a pesticide. These are noted as Required (R), Conditionally Required (CR), or Not Required (NR) for each use pattern. The toxicologist alerts their company's regulatory manager to the required toxicology studies as well as the expected cost and time line for completion. Table 9.3 lists categories of Office of Chemical Safety and Pollution Prevention (OCSPP) harmonized test guidelines.

Hazards can also be identified by reliable epidemiological studies (Roberts & Reigart, 2013) as well as peer reviewed literature. Epidemiology data are valuable in that they can help to inform potential effects in humans but quantitative characterization of the exposure in these studies is generally insufficient for direct use as a toxicity endpoint in risk assessment. The Agency is actively exploring how to use epidemiology data in both hazard and risk assessment for pesticides. These include the Tox21 program that uses high-throughput robotic screening and ExpoCast that estimates population exposure. The Toxicology in the 21st Century (Tox21) approach targets specific bioactivity at the molecular or cellular level. Concentration-response data from multiple assays can be integrated mathematically in a computational model to provide a chemical's bioactivity in that pathway (by example, the estrogen receptor pathway).

The OCSPP 870 Test Guideline Series provide detailed information on study designs for assessment of health effects and include acute, subchronic, reproductive and developmental, chronic,

TABLE 9.3
OCSPP Harmonized Test Guidelines

Series Number	Series Name	Docket ID No. EPA-HQ-OPPT-2009-xxxx
810	Product Performance Test Guidelines	0150
830	Product Properties Test Guidelines	0151
835	Fate, Transport and Transformation Test Guidelines	0152
840	Spray Drift Test Guidelines	0153
850	Ecological Effects Test Guidelines	0154
860	Residue Chemistry Test Guidelines	0155
870	Health Effects Test Guidelines	0156
875	Occupational and Residential Exposure Test Guidelines	0157
880	Biochemicals Test Guidelines	0158
885	Microbial Pesticide Test Guidelines	0159
890	Endocrine Disruptor Screening Program Test Guidelines	0576

genotoxicity, and neurotoxicity testing along with some special studies. EPA promulgates guidelines for these and other studies. These guidelines have footnotes that clarify when each test must be conducted. Understanding the basis for these tests in conjunction with the use pattern forms the basis of waivers, when appropriate.

The EPA and the Organization for Economic Cooperation and Development (OECD) provide guidelines for studies that characterize chemical hazards. The Agency's OCSPP 870 series address acute, subchronic, chronic, developmental and mutagenicity testing. These guidelines have footnotes that clarify when each test must be conducted. Understanding the basis for these tests in conjunction with the use pattern forms the basis of waivers, when appropriate.

Specific areas that the agrochemical regulatory toxicologists might be responsible are noted in the following. Front and center are the Health Effects. Summaries based on excerpts from Agency follow. Common to most studies are control groups and three or more treatment groups. Goals include establishing the Lowest Observed Adverse Effect Level (LOAEL), No-Observed-Adverse-Effect Level (NOAEL), and limit dose (LD).

Acute Studies

Determination of acute oral, dermal and inhalation toxicity in surrogate species is often the initial step in the assessment and evaluation of the toxic characteristics of a pesticide. These data provide information on health hazards likely to arise soon after, and as a result of high dose, short-term exposure. Data from acute studies serve as a basis for classification and precautionary labeling and determine the need for child resistant packaging. Information derived from primary eye and primary dermal irritation studies serves to identify possible hazards from exposure of the eyes, associated mucous membranes and skin. Acute toxicity also serves to inform what Personal Protective Equipment (PPE) should be required for handling these products. The acute toxicity studies can be used as a starting point for establishing the appropriate dose levels in subchronic and other studies and may provide initial information on the mode of toxic action of a substance.

The goal of reducing animal usage has led to alternative approaches or protocol refinements that obtain the necessary regulatory data. By example, the Up-and-Down procedure (test guideline 425) uses less animals than the standard LD_{50} study. The EPA is also using an Integrated Approach to Testing and Assessment (IATA) to enhance risk and management decisions. Their retrospective analysis and guidance for waiving acute dermal toxicity tests will further reduce animal usage as appropriate waivers are encouraged. The use of *in vitro* alternatives for acute toxicity testing in place of the traditional animal testing is also an Agency priority.

Subchronic Studies

While acute studies typically use a single dose of test material, subchronic tests require multiple dosing regimens. In general, these include a control and three treatment levels. For the study to be acceptable, the treatment levels must include a NOAEL as well as the LOAEL. Repeat dose studies provide information on health hazards that may arise from repeated exposures over a limited period of time (short-term and intermediate-term exposures). The appropriate route of administration may be oral (dietary), dermal or inhalation. They provide information on target organs and toxicological mode of action. The resulting data are also useful in selecting dose levels for chronic studies and for establishing safety criteria for human exposure.

Metabolism studies along with pathologic evaluations are components in elucidating modes of action. Other parameters include metabolic changes (enzyme, hormone and electrolyte levels) as well as recovery studies. Determining systemic dose by collecting and analyzing blood in these studies is gaining traction to aid the understanding of pathological evaluation and dose selection for chronic studies. The collective data are also useful for establishing points of departure (POD) for human risk assessment.

Chronic Studies

Chronic toxicity studies are intended to determine the effects of a substance in a mammalian species following prolonged and repeated exposure. Chronic rodent studies are generally two years in rats and 18 months in mice. Effects that have a long latency period or are cumulative should be detected. The purpose of long-term carcinogenicity studies is to observe test animals over most of their life span during exposure to various doses of a test substance by an appropriate route of administration, typically oral dietary exposure. These studies are among the most expensive to conduct. Efforts have been made to obtain meaningful data without the need for full two-year studies. By example, six-month studies, with the appropriate end-points, may be predictors of carcinogenicity should the test be extended to two years (Reddy et al., 2010).

The elucidation of mode of action is important which may distinguish between mutagenic and non-mutagenic carcinogens. Where step-wise mode of actions (MOAs) are identified, evaluation of human relevance of these findings is of importance (e.g., thyroid tumors in male rats) (Capen, Dybing, Rice, & Wilbourn, 1999).

Developmental and Reproductive Toxicity

The developmental toxicity study, often referred to as a teratogenicity study, is designed to determine the potential of the test substance to induce structural and/or other abnormalities to the fetus as the result of exposure of the mother during pregnancy.

These studies expose pregnant females (usually both rats and rabbits are tested) during the gestation phase. During these studies, the test compound is typically administered orally by gavage. Altered growth in offspring is reflected in organ or body weight or size. Structural abnormalities include malformations and variations. A malformation is a permanent structural change that may adversely affect survival, development, or function. Variations indicate a divergence beyond the usual range of structural constitution that may or may not adversely affect survival or health.

For rodents, approximately one-half of each litter are prepared by standard techniques and examined for skeletal alterations, preferably bone and cartilage. The remainder should be prepared and examined for soft tissue anomalies, using appropriate serial sectioning or gross dissection techniques. Fetuses can also be examined by careful dissection for soft tissue anomalies followed by examination for skeletal anomalies.

For rabbits, all fetuses should be examined for both soft tissue and skeletal alterations. The bodies of these fetuses should be evaluated by careful dissection for soft-tissue anomalies, followed by preparation and examination for skeletal anomalies. An adequate evaluation of the internal structures of the head, including the eyes, brain, nasal passages, and tongue, should be conducted for at least half of the fetuses.

In these studies, it is a necessity to pay close attention to maternal toxicity, which may cause secondary adverse effects to offspring.

Developmental and reproductive NOAELs are sometimes identified as being the most sensitive toxicity endpoint for use in risk assessment (Acute Reference Dose [aRfD] and Chronic Reference Dose [cRfD]) and incidental oral PODs. The rabbit differs from the rat regarding nutrition and its sensitivity to handling. Rabbits rely on re-ingestion of cecotropes, termed *night stools*. These are distinct from fecal pellets and are softer, greener, and have a stronger odor than the normal hard, dry, round waste droppings. They come directly from the cecum. In the cecum, the digestible portion of the diet is broken down by bacteria, which then product fatty acids, amino acids, vitamins, and minerals. They are necessary for adequate nutrition of the dam. Compounds that disrupt the bacterial flora of the rabbit may adversely affect the dam's health and, secondarily, the development of pups (Gordon, Neal, & Ehrlich, 2007).

Reproduction testing can be conducted for one (extended one generation) or two generations. These studies are designed to provide information concerning the general effects of a test substance on gonadal function, estrus cycles, mating behavior, conception, parturition, lactation, weaning, and the growth and development of the offspring. The extended one generation study also evaluates

immunotoxicological and neurotoxicological endpoint in the offspring. The rat is commonly used for reproductive testing and exposure to the test materials is typically oral through the diet.

Genetic Toxicity Studies

A battery of tests is required to assess the potential of test materials to affect the mammalian cell genetic components. The objectives underlying the selection of a battery of tests for genotoxicity assessment include the detection of a chemical to alter genetic material in cells; and determine the relevance of these changes to mammals. Both *in vitro* and *in vivo* tests are conducted.

Tests include bacterial reverse mutation assay (the *Ames test*), *in vitro* mammalian cell assay, and *in vivo* cytogenetics. The Ames test uses several strains of the bacterium Salmonella typhimurium that carry mutations in genes that are involved in histidine synthesis. Mutations are evident when bacteria are able to grow in histidine-fee medium. Many potential carcinogens can be detected with this test. *In vitro* mammalian cell assays, such as the mouse lymphoma assay, detects forward mutations. In vivo cytogenetic studies are designed to test affects in mammalian germ cells (numerical and structural chromosome aberrations, sister chromatid exchanges, aneuploidy in mature sperm and other endpoints). Additional genotoxicity studies can be conducted to evaluate the potential for genotoxicity in additional tissues or *in vivo* mutagenicity.

It is important to identify compounds that cause mutations *in vitro* but do not cause mutations *in vivo*. This can be due to inactivation of chemicals when given *in vivo* or absence of systemic exposure due to lack of absorption and/or extensive hepatic recirculation. Compounds that cause tumors in rodents and are also mutagenic *in vivo* will be labeled mutagenic carcinogens unless data support a non-mutagenic MOA.

Metabolism Studies

Data from the absorption, distribution, metabolism, and excretion studies (ADME) of a pesticide (toxicokinetics) aid in dose selection, the establishment of a maximum tolerated dose level (MTD), the evaluation of test results from other toxicity studies, and in the extrapolation of data from animals to man. The main purpose of metabolism studies is to produce data that increase the EPA's understanding of the behavior of the chemical when considering the human exposure anticipated from intended uses of the pesticide. Specifically, ADME studies help elucidate the mode of action of the active ingredient (see the Modes of Action section). Recent improvements in the guidelines recommend conducting *in vitro* metabolism using tissue (mostly liver) fractions (e.g., homogenates, S9, microsomes) of all test species for comparison with human tissue fractions. These reflect advances in drug development (Zhanga, Luob, Dingc, & Lu, 2012).

Modes of Action

Understanding the MOA of an active ingredient is key to establishing relevant risk assessments for the human population (Dellarco, 2008). Mechanisms of toxicity have been described as a sequence of events, each of which is critical to the evolution of the toxic effect (ECETOC, 2006). Complete elucidation of all events is not required if one can identify a key event that distinguishes one species (test animal) reaction to another (humans) (qualitative non-relevance to humans). By example, kidney tumors in rats caused by d-limonene were shown not to be relevant to humans (Flamm & Lehman-McKeeman, 1991). Liver tumors in rats may not be relevant for human risk assessment depending on the specific MOA (Holsapple et al., 2005). Elucidation of the mode of action of the fungicide captan allowed the EPA to revise its carcinogenicity category from B2, *likely* to *not likely* under the conditions of exposure (Gordon, 2007). In the case of captan, clear mutagenic effects *in vitro* were not replicated *in vivo*, due to rapid degradation of the active ingredient. Other actions, in this case prolonged irritation of the duodenal villi, accounted for the eventual development of intestinal tumors. This MOE was judged not relevant to humans, based on exposure levels. Once MOAs are clearly established, meaningful human risk assessments are facilitated. Significant resources, however, are often needed for full elucidation of MOAs.

Hazards to Nontarget Organisms

Apart from the Series 870 requirements, OCSPP Series 850 address hazards to nontarget organisms derived from tests to determine pesticidal effects on birds, mammals, fish, terrestrial and aquatic invertebrates, and plants. These tests include short term acute, subacute, reproduction, simulated field, and full-field studies arranged in a hierarchical or tier system that progresses from the basic laboratory tests to the applied field tests.

Endocrine Disruption

FQPA encapsulated Theo Colborn's (1927–2014) concerns with endocrine disrupting chemicals and required the EPA to consider such information "as the Administrator may require on whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects" (US Congress, 1996). OCSPP 890 series encapsulate the endocrine disruption-screening program (EDSP), which was launched to address the FQPA mandate. EDSP is a two-tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems. Tier I studies provide screening data for the active ingredients for endocrine activity and Tier II studies are designed to characterize definitive endocrine effects. All pesticides will eventually undergo Tier I screening. EPA's Tox21 program is important here as well, and the Agency intends to use Tos21 and ExpoCast to prioritize additional pesticides for endocrine testing.

Dose Response

Establishing the NOAEL is essential. The dose-response curve characterizes the relationship of systemic exposure to adverse effects which is used for the risk assessment. The Agency typically applies safety factors to the NOAEL to arrive at acute and chronic reference doses (aRfD, cPAD) for the general population. In the absence of a NOAEL, the Agency uses LOAEL for the calculation of the reference dose by applying additional safety factor(s). Selection of endpoints in test animals should be relevant to humans. The Agency encourages the use of the benchmark dose (BMD) analysis for establishing key risk assessment reference doses (US EPA, 2012a). The benchmark dose approach was developed as an alternative to the NOAEL/LOAEL approach for risk assessment. BMD analysis determines the studies and endpoints on which to base the BMD calculations; selection of the BMD value; choice of model to use in computing the BMD; model fitting; computation of confidence limits; and, arriving at recommendations for presentation of the BMD and BMD Lower bound (BMDL) computations.

Exposure Assessment

Accurate exposure data are essential for reliable risk assessments. Data are used to evaluate exposures to persons in occupational and non-occupational settings, including agricultural, residential, commercial, institutional, and recreational sites. Data include oral, dermal and inhalation exposure data, post-application residue data, post-application monitoring data, use information, and human activity information. Occupational exposure applies to mixer/loaders and applicators as well as re-entry workers. Residential exposure reflects the pesticide exposure to homeowners who use pesticides while dietary exposure requires accurate residue levels in foods along with food consumption data. Pesticide tolerances (maximum allowable residue levels, MDLs) are established based on residue trials and the respective toxicology of the active ingredient.

Occupational Exposure

Data are used to evaluate exposures to persons in occupational settings. These data, together with toxicology data, are used to determine whether application or post-application risks are of concern. Restrictions, in days, for workers reentering treated fields, are influenced by the hazards of the

active ingredient and serve to maintain occupational exposure at acceptable levels. The degradation of residues due to sunlight and other environmental conditions (e.g., rainfall) impacts the risk to reentry workers; thus, faster degradation curves may shorten the reentry interval required.

EPA has relied on the Pesticide Handler Exposure Database (PHED) but is upgrading these data with inputs from a number of industry task forces. Both PHED and data from these task forces provide unit exposure values for different scenarios based on the pounds of active ingredient handled. These exposure values are provided in µg/lb a.i. and apply to both dermal and inhalation exposure. By example, a mixer loader handling granular material will have a certain µg/lb a.i. dermal exposure and a µg/lb a.i. inhalation exposure. The current exposure values are noted in the Agency's Occupational Pesticide Handler Unit Exposure Surrogate Reference Table.

The Agricultural Reentry Exposure Task Force (ARTF) generates exposure data for re-entry workers who harvest, scout, or conduct other operations in the field. The Outdoor Residential Exposure Task Force (ORETF) generates data primarily for products applied to residential setting (e.g., lawns) and the transfer of residues to persons contacting treated lawns due to the residues. The Agricultural Handler Exposure Task Force (AHETF) is generating data on exposure to mixer/loaders and applicators. As these data are accepted, they are entered into the Occupational Pesticide Handler Unit Exposure Surrogate Reference Table.

These task forces have expended significant resources. By example, AHETF's cumulative budget as of 2016 is more than $50,000,000. FIFRA protects this investment by requiring companies that wish to use these data to pay compensation to the respective task forces. If the company you represent has not been a task force member, be certain to alert management that substantial compensation issues may arise if they need to rely on these data. The Occupational Pesticide Handler Unit Exposure Surrogate Reference Table indicates whether the unit exposure is based on PHED or the task forces. PHED data are not compensable; task force data are compensable for a period of 15 years. Compensation issues apply to all studies used to support registrations.

Dietary Exposure

Dietary risk from oral exposure is based on established residue tolerances. *Standard food intakes* determine the exposure to active ingredient residues. Acceptable Daily Intakes (ADIs) are based on information that includes data on the biochemical, metabolic, pharmacological and toxicological properties of the pesticide. The Theoretical Maximum Daily Intake (TMDI) is a screening tool for assessing dietary intake. The World Health Organization (WHO) notes that the TMDI is the sum of the Maximum Residue Limit (MRL) for a given food commodity times the per capita global Environment Monitoring System (GEMS) food regional consumption of that food. The EPA uses models that include the Dietary Exposure Evaluation Model (DEEM) and the Dietary Risk Evaluation System (DRES). Probabilistic techniques are used in these assessments.

Dermal Absorption

The degree of dermal absorption for occupational workers is often factored into occupational and non-occupational risk assessments. Dermal is the primary exposure route; inhalation, by comparison, is minor. Dermal absorption studies are typically conducted when a non-dermal endpoint is used as the POD for dermal risk assessment. The DAF is used to modify the default 100% dermal absorption assumed by the Agency in assessing occupational and residential dermal risk. Rat skin is generally more permeable than human skin. Studies measuring dermal absorption *in vivo* in rats and an *in vitro* comparison with human and rat skin, referred to are the triple pack protocol, have been developed to estimate the dermal absorption factor (DAF) for humans (OECD, 2010). The OECD has guidance on the conduct and interpretation of triple pack studies; however, the interpretation of the triple pack is not harmonized between the global regulatory Agencies. Be aware that there are often different DAFs from multiple studies and a clear rationale for choosing one needs to be supported. Agencies tend to be conservative, in keeping with their mission. Where single

in vitro studies (versus the triple pack) adequately reflect human absorption, these allow streamlined assessment. Currently, however, the Agency requires the triple pack.

Aggregate and Cumulative Exposure

FQPA requires that exposure from all sources be considered when conducting risk assessments. Aggregate exposure and risk assessment involve the analysis of exposure to a single chemical by multiple pathways and routes of exposure. These include residues in food and drinking water, as well as residues from pesticide use in residential, non-occupational environments. The pathway of exposure refers to how human behavioral patterns potentially interact with pesticides in the environment. Routes of exposure include oral, dermal, and inhalation.

Cumulative exposure represents exposure to different active ingredients that are found to have a common mechanism of toxicity (CMT), for example, organophosphates (US EPA, 2002). Organophosphates were the subject of an Agency cumulative risk assessment (US EPA, 2015c). Where a CMT has not been determined by the Agency, individual active ingredients are assessed separately. Worker risk assessments integrate both aggregate and cumulative exposures, where applicable (US EPA, 2016b).

FQPA requires that exposure from all sources be considered when conducting risk assessments. Aggregate exposure and risk assessment involve the analysis of exposure to a single chemical by multiple pathways and routes of exposure.

Models

There are a number of Agency models that help estimate exposure. The Center for Exposure Assessment Modeling notes a number of these (US EPA, 2015b). Dietary Exposure Evaluation Model (DEEM) is used to estimate exposure to pesticides in foods in the diets of the US population. The Exposure Related Estimating Model (ERDEM) is a physiologically based pharmacokinetic (PBPK) and pharmacodynamics (PD) modeling system that describes the disposition of a chemical in the body (Blancato, Power, Brown, & Dary, 2006).

Risk Characterization

The process of risk characterization integrates hazard, dose-response and exposure to determine the level of risk. The objective is to ensure *certainty of no harm* will occur through the use of the pesticide. The risk characterization document is where "the rubber meets the road" for regulatory toxicologists. Toxicologists should anticipate pushback from regulators when these are not addressed clearly.

Safety Factors/Uncertainty Factors

Traditionally, two *standard* uncertainty factors (UFs) of 10X each have been applied to account for interhuman variation (intraspecies) and experimental animal to human (interspecies) differences. These intraspecies an interspecies UF have also been broken down to toxicokinetic and toxicodynamic factors. Thus, a 100X UF applied to a NOAEL of 10 mg/kg bw/day results in a 0.1 mg/kg bw/day reference dose (RfD). This 100X would take a NOAEL of 10 mg/kg bw/day to obtain a 0.1 mg/kg bw/day reference dose. In some instances, additional UFs can be applied to account for database deficiencies, for example, absence of a NOAEL; absence of key data.

With the passage of FQPA, *special FQPA* safety factors were introduced to address "residual concerns for susceptibility and residual concerns in the exposure assessment." FQPA safety factors can vary from 3X to 10X depending on the level of uncertainty and the data deficiency. When standard and FQPA factors are combined, the reference dose could be 1000X below the NOAEL and often necessitates refinement of exposure estimates to achieve an acceptable risk assessment. In addition, *susceptible populations*, such as infants and children (pediatric population), may require additional uncertainty factors. Susceptibility is defined as a capacity characterized by biological

(intrinsic) factors that can modify the effect of a specific exposure, leading to higher health risk at a given relevant exposure level. The term sensitivity is used to describe the capacity for higher risk due to the combined effect of susceptibility (biological factors) and differences in exposure. Vulnerability incorporates the concepts of susceptibility and sensitivity, as well as additional factors that include social and cultural parameters (e.g., socio-economic status and location of residence) that can contribute to an increased health risk.

AGROCHEMICAL RISK MANAGEMENT

Risk management's goal is to refine unacceptable risks so that they become acceptable. Typically, this is done by refinements of product formulation, use scenarios, and requirement of appropriate PPE. There are two categories of risk management: occupational and dietary. For food-use agrochemicals, both occupational and dietary risk need to be acceptable. Occupational risks are associated with mixer/loader and applicators; dietary risks are associated with residues on foods. Options for refining dietary exposure are described in the following.

Occupational Risk Management

Occupational risks can be refined by changes in product formulation, mixing scenarios, and PPE. The exposure to occupational workers is refined by a number of industry task forces. The Spray Drift Task Force characterized how the size of droplets affected the drift of aerial applications (Hewitt, Johnson, Fish, Hermansky, & Valcore, 2002). The ARTF characterized the dermal and inhalation exposure to workers involved in a variety of fieldwork, such as harvesting, scouting, and tying vines. The Outdoor Residential Exposure Task Force (ORETF) characterized the transfer of residues from turf to persons contacting the grass. The Agricultural Handler Exposure Task Force (AHETF) characterizes exposure to mixer/loader and applicators under various scenarios (fieldwork completion by 2017).

Each of these Industry Task Forces has worked closely with the EPA to ensure the data generated meet the Agency's needs. With the advent of the Human Studies Rule all AHETF study protocols and monographs have been reviewed by Institutional Review Boards (IRBs) and approved by the Human Studies Review Board (HSRB). The results of these studies have been integrated into the Occupational Pesticide Handler Unit Exposure Surrogate Reference, which reflects both Pesticide Handler Exposure Database (PHED) and newer *more reliable* task force data.

Product Formulation

Unit exposures are based on the pounds of active ingredient handled. A given exposure to occupational workers will vary depending upon the formulation; whether the product is a granule, or in liquid formulation.

Significant reduction in exposure potential to mixer/loaders may also be obtained if the active ingredient is packaged in water-soluble packets. These packets have pre-measured amounts of active ingredient and are dropped directly into the mixing container avoiding direct handling of the active ingredient. Other reductions in exposure may be obtained through the use of drip irrigation and ready-to-use (RTU) formulations.

Mixing Scenarios

Mixing scenarios are generally open or closed systems. For closed systems, the exposure to mixer/loaders is markedly reduced, as they do not directly handle the active ingredient. An unacceptable occupational risk in an open mixing/loading scenario will usually be acceptable if the system is closed.

Personnel Protective Equipment

Base PPE includes long sleeved shirt, long pants, shoes with socks, and gloves. Unit exposures decrease when a double layer of clothing is donned and gloves are worn. Wearing respirators reduces inhalation exposure. Unit inhalation exposures are decreased when respirators are donned. Protection Factors (PF) indicate the exposure protection of each respirator. By example, a PF5 respirator provides an 80% reduction in inhalation exposure and a PF10 provides a 90% reduction. These protection factors depend, however, on proper use (good fit, respirator maintenance, cleanliness, and use of appropriate cassettes).

Reentry Interval

Reentry workers conduct a variety of tasks associated with farming: harvesting crops, scanning for pests, tying vines, and so on. Each of these tasks is associated with a transfer of residues to the clothing or skin of the workers. The ARTF conducted many studies that measured the degree of such transfer. The agrochemical residues on crops decrease with time. Reentry intervals take this decline curve into account.

Dietary Risk Management

Pesticide residue levels are used to set acceptable tolerances. If new formulations are developed that apply lower amounts of active ingredients, follow-on residue trials would be required to set new tolerances.

Risk Communication

It is not enough to do *good science*. Toxicologists must be articulate and believable both to the Agency and to the public. Toxicologists must keep mind that many activists' groups believe agrochemicals are bad and should be banned no matter the data or how many studies are performed proving their safety. Themes of these activists' groups include unnecessary killing of animals, promoting poisons and pesticides causing cancers. Therefore, it is not sufficient to know the facts, but also communicate with them in a believable, sound way. The Agency has noted the importance of sound risk communication (US EPA, 2016c).

Toxicologists routinely communicate risk to deal with FIFRA 6(a)(2) incidents whether as a follow-up with persons who have suffered adverse effects or simply asked questions about the toxicity of one of the products.

CONSIDERATIONS FOR THE AGROCHEMICAL TOXICOLOGIST

Active Ingredient

Toxicologists deal with registration issues either of a new active ingredient (a.i.) or stewardship of the one already in the market. For new active ingredients, the challenge is to build a database from scratch. For existing active ingredients, the first step is to assimilate all relevant data that describe the toxicity and known issues and study previous EPA and other agencies (e.g., WHO, EFSA) reviews. The goal of Toxicologists is to become the definitive resource for all toxicity issues related to the a.i. in question.

Pre-Application Meeting

Pre-application meetings are opportunities to clarify data requirements for the use scenario sought which are arranged mostly by the registration managers of agrochemical companies. Toxicologists

need to review available toxicology data on the a.i. prior to such meetings, prepare an outline of registration requirements, contribute to the agenda that will be sent to the product manager of the agency prior to the meeting, and request that key agency personnel be in attendance to resolve specific issues when warranted.

Common discussion points could include data waivers, additional studies to elucidate a mode of action, food or non-food use, PRIA category specifying fee, and timeline for application review.

Pesticide Registration Improvement Extension Act (PRIA 3)

PRIA establishes fees for registration and the timelines the Agency is required to meet. These fees are periodically reviewed and revised, for example, PRIA 3. While regulatory associates primarily handle this, toxicologists should be cognizant of the costs and timelines involved.

Waivers

Well-crafted data waivers are important in the registration process. A waiver that successfully convinces the Agency that a study is not needed will save both time and money for the company or client. These savings can be substantial depending on the specific study requested by the Agency. Toxicologists need to be sure to follow mandated formats for these and all study submissions (US EPA, 2012b). Ethical considerations are often integrated into waivers as an effort to reduce the excessive use of vertebrate animals in studies as part of 3Rs (Replacement, Reduction, Refinement) goals (University of Minnesota, 2003).

Before embarking on writing a waiver, consider the following. Do the footnotes for the 40 CFR part 158 requirements cover the end-use scenario? Are the points of departure for risk assessment going to be influenced by conducting this study? Is any new toxicological data going to be available by conducting this study? Does the requirement, if based on a Data Call-In (DCI), cite an Agency risk assessment? If so, be sure to review the risk assessment document to see if the analysis is reliable. Does the Agency routinely accept waivers for the particular study in question? By example, immunotoxicity studies, while previously required, are now routinely waived, based on a retrospective analysis of whether or not these data actually affected the Agency risk assessments (Rowland, 2013). Look for precedents in Agency documents that support your waiver. A face-to-face meeting with the Agency may help to present your rationale for the waiver.

Electronic Submissions

New applications may be submitted using the Central Data Exchange (CDX) portal. This offers significant efficiency in file preparation, submission, and milestone status updates. Three hard copies of each study are no longer required. Regulatory associates of the company normally make these submissions.

Efficacy Data

Efficacy data must be developed and submitted to the Agency for antimicrobial pesticides. Regulatory toxicologists do not generally develop these data. Efficacy data must also be available for submission to the Agency if it is required for other uses (e.g., insecticides, fungicides, herbicides). Efficacy are developed during the initial product development. It obviously is counterproductive to market an end-use product that doesn't work as promoted.

Study Monitoring

When monitoring studies at CROs toxicologists, need to develop good communications with the study director and management. It is helpful to have previous experience as a study director. Toxicologists need to appropriately communicate these discussions with the regulatory staff, so they are apprised of the integrity of the study and the expected completion date and availability of the final report. Review of draft reports by toxicologists in a timely fashion is critical in meeting deadlines. Toxicologists conduct iterative risk assessments with probable NOAELs. Proper study monitoring with attention to detail is essential to assure meeting global requirements and reducing the needs to repeat studies. Additionally, toxicologist need to assure a level of peer review early in the study process.

Study acceptance when a study is reviewed by the Agency is essential. The study, however well performed, will not be accepted unless the protocol addresses all Agency requirements. For some studies, the Agency encourages meetings to ensure the study protocol is acceptable. Some 90-day studies may be addressed with a shorter 28-day study (e.g., inhalation). Be sure to explore what study refinements can be made to shorten the time required and associated costs.

Review OPPTS guidelines. In vetting laboratories for your work, ask the respective study directors if they have, with Agency approval, modified the OPPTS guideline.

Good Laboratory Practice Regulations

Good Laboratory Practices (GLPs) Regulations were instituted following instances of fraudulent data in a contract research laboratory (NY Times, 1983). These regulations were promulgated to support the integrity of data submitted to the Agency (US EPA, 2014). Where the option of conducting studies under GLP or non-GLP (at lower cost) exist, opt for GLP. If a study is going to be submitted to an agency or used to provide preliminary data in support of dose selection, the initial cost savings if non-GLP may haunt you in the future.

Flagging Criteria and FIFRA 6(a)(2) Reporting

The Agency specifies criteria that require *flagging* in final reports. Table 9.4 lists these. Toxicologists review each final report to ensure such criteria are cited, when required.

Apart from flagging criteria that alert the Agency to new findings, FIFRA 6(a)(2) reporting requirements identify adverse effects that were not identified during the registration process (US EPA, 1998). These adverse findings cover human exposure, domestic animals and wildlife, findings in toxicology studies that lower previous NOAELs, and other incidents that the Agency considers important. For incidents that are *minor*, collect incidents over a three-month period and submit a summary report to the Agency within 60 days. For major incidents, reporting times are shortened. If the known effect, such as paresthesia, is noted on the Label, reports are not required. A Committee should be formed to review any questionable submissions. Committee deliberations and conclusions need to be logged in the event the Agency questions why a particular report was not made.

Petition for Registration

Usually, regulatory associates will prepare and submit the registration application. Toxicologist's input is required for the Confidential Statement of Formula (CSF) and other EPA required forms. It is often helpful to prepare an overview document, with toxicology input, which includes the

TABLE 9.4
Flagging Criteria

Study Type(s)	Guideline No.	Criteria: Treated Animals Show Any of the Following:	Criteria No.
Carcinogenicity or combined carcinogenicity/chronic feeding	870.4200 870.4300	An incidence of neoplasms in males or females which increases with dose (positive trend $p \leq 0.05$); or	1
		A statistically significant (pairwise $p \leq 0.05$) increase of any type of neoplasm in any test group, males or females at any dose level, compared to concurrent control animals of the same sex; or	2
		An increase in any type of uncommon or rare neoplasms in any test group, males or female animals at any dose level, compared to concurrent controls of the same sex; or	3
		A decrease in the time to development of any type of neoplasms in any test group, males or females at any dose level, compared to concurrent controls of the same sex	4
Prenatal developmental toxicity; reproduction and fertility; developmental neurotoxicity	870.3700 870.3800 870.6300	When compared to concurrent controls, treated offspring show a dose-related increase in malformations, pre- or post-natal deaths, or persistent functional or behavioral changes on a litter basis in the absence of significant maternal toxicity at the same dose level	5
Neurotoxicity	870.6100 870.6200	When compared to concurrent controls, treated animals show a statistically or biologically significant increase in neuropathological lesions or persistent functional or behavioral changes	6
Chronic feeding; Carcinogenicity; Reproduction and fertility; Prenatal developmental toxicity; Developmental neurotoxicity; Acute or 90-day neurotoxicity	870.4100 870.4200 870.3800 870.3700 870.6300 870.62.00	The no-observed-adverse-effect level (NOAEL) from one of these studies is less than the NOAEL currently used by the Agency as the basis for either the acute or chronic reference dose	7

regulatory objective, active ingredient mode of action, use scenarios, and draft occupational and dietary risk assessments. Such summaries help with waiver development and support the purpose and usefulness of the proposed end-use formulation.

Budgets and Timelines

Registration personnel need to know realistic estimates of data development costs as well as timelines for obtaining final reports. Best-case scenarios are subject to many opportunities for delay and increased costs. Incorporation of some buffer estimates for both final costs and report deadlines is essential in most cases. Proper logistics for the delivery of test materials and prompt resolution of issues arise during the conduct of the study. It is essential to avoid delay in final reports.

The Study Director at the CRO has an opportunity to become an extension of the Sponsor such that he or she becomes a trusted advocate for the Sponsor within the CRO. As an advocate, the Study Director can manage CRO deliverables and communicate information to the Study Monitor

in *real time*. By providing scientific input and troubleshooting suggestions, the *integrated Study Director* ensures that the Sponsor's objective timelines are kept front and center.

Experts

As regulatory toxicology advances, generalists have difficulty handling all the problems that require in depth knowledge. Development of a cadre of experts for assistance in areas such as Quantitative structure-activity relationship, developmental toxicity, mutagenicity, immunotoxicity, and endocrine disruption is helpful.

Inerts

Inert or *other ingredients* in the formulations also need to be approved for use by the Agency if they are not already listed as approved (US EPA, 2015e). If they are not listed, then an Inert Petition needs to be submitted for review. An in-depth toxicology review of the inert ingredient used in the formulation is required for this petition.

Formatting

All submissions to the Agency (Final Reports, Waivers, Petitions) need to be formatted in accordance with Pesticide Registration (PR) Notice 2011-3 (US EPA, 2012b). Specific instructions relate to the Title Page, Page 2 (Statement of Confidentiality Claim), Page 3 (Statement of compliance or non-compliance with good laboratory practice standards) and Page 4, if necessary, flagging of studies for potential adverse effects. The Agency conducts initial formatting checks, which will reject submissions that do not conform. Insure, also, that pagination is accurate.

CONCLUSION

The regulatory toxicologist specializing in agrochemicals needs to integrate the mandated science requirements for registration with FIFRA-based Agency application needs. Toxicologists need to keep in mind the regulatory goals and work forthrightly with registration specialists and the Agency representatives.

A toxicologist's job integrates science, management, and creativity for attaining your regulatory goals. A regulatory toxicologist's work is challenging, interesting and rewarding. Pesticide toxicology presents an array of projects, each a new learning experience and each an opportunity to broaden the horizon of knowledge. Enjoy the journey.

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10 Industrial Chemicals Regulation of New and Existing Chemicals (The Toxic Substances Control Act and Similar Worldwide Chemical Control Laws)

Sol Bobst and Richard C. Kraska

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INTRODUCTION

In the major developed countries, laws to regulate chemicals used as drugs, food additives and pesticides were developed first due to public health and environmental concerns of these uses. Eventually these laws required pre-market clearances of new chemicals for these uses. As time went on, laws were implemented so that virtually all chemicals had some level of regulation. Chapters 10 and 11 deal with the laws that affect the industrial chemical industry. This chapter deals with the so-called chemical control laws, which affect the introduction of new chemicals into commerce as well as attempt to manage newly discovered risks of existing chemicals. The next chapter deals with laws concerning worker safety, which govern the communication of the hazard information and establish safe exposure levels for chemicals. This chapter includes additions since the last version of this publication based on new legislation and programs, and the format of the chapter has been retained to emphasize the historical development of the regulations and requirements over time. Key updates include major legislation changes since the last edition of this book.

Globally, the major chemical control laws include provisions for premanufacture or premarketing clearance for new chemicals. In addition, these laws contain various provisions for reporting information and controlling the risk of all chemicals, including preexisting chemicals that were in commerce before notifications for new chemicals were required. Legal, procedural and public policy analysis of these statutes is a fascinating subject covered adequately elsewhere (CEQ, 1971; EPA, 1996, 1997; OECD, 1997a, Bergeson et al., 2000). This chapter will focus on the health and environmental issues with an emphasis on recent trends in these issues because they are of primary interest to toxicologists. In addition, the issues of interest to toxicologists are very complex and have many exceptions depending on the nature of various chemicals. Toxicologists need to consult the regulations, guidance documents and the experience of other practitioners in order to truly become an expert in the requirements of chemical control laws.

General Overview

The first of these laws was passed in certain countries that experienced toxic incidents or concern about public and environmental health associated with the use and disposal of industrial chemicals.

As time went on, other countries enacted similar laws, attempting to customize laws to national concerns and correct perceived defects in the laws they sought to emulate and improve upon.

Each of these laws defines a regulated community that usually consists of manufacturers and importers of chemicals. The laws give regulatory and enforcement authority to one or more national federal agencies. Since there were decades of industrial activity to reconcile, the laws commonly empower the agencies to require the regulated industry to report various information about manufacture and use of the chemicals as well as unpublished health and safety information about chemicals and processes.

Historically, it has been difficult for practitioners to get information about requirements in other countries. This has improved with information now available on the Internet and general trends in globalization. A list of useful websites is given at the end of this chapter. Available guidelines and other publications will be mentioned at the appropriate points in this chapter. Another good source of information is the Organization for Economic Cooperation and Development (OECD). This organization has provided a platform for international discussion of a variety of issues associated with the regulation of chemicals and the work products of many work groups contribute significantly to the information available on many issues.

New regulations, including the European Union's (EU) Registration, Evaluation, Authorization and Restriction of (REACH) regulation and the Lautenberg Chemical Safety Act (TSCA reform), are the result of increasing public interest in chemical safety. The increased access to public information via the internet and social media has created pressure for regulations to be modernized to reflect business and consumer behaviors in the globalized marketplace and economy.

REQUIREMENTS FOR NEW CHEMICALS

Overview

Before any of the authority for requiring applications or notifications from industry to clear new chemicals for manufacture or marketing was implemented, each regulatory authority was required to establish a list or inventory of chemicals already in use. Usually this required several years of reporting by the regulated industry followed by compiling, publishing and correcting the list by the regulatory agency. Many chemical control laws established their inventories using the nomenclature system of the Chemical Abstract Service (CAS) and the CAS registry numbers assigned by this service.

The intricacies of the listing process and the various exemptions and notification procedures for various classes of new chemicals is usually of high interest to regulatory chemists and attorneys, but beyond the scope of this chapter. Consult the regulations in each country for these details. Another good source of great detail on the subject is the report of an OECD workshop on sharing chemical assessments between regulatory authorities (OECD, 1997a) and the New Industrial Chemicals Information Directory (OECD, 2000).

The testing and evaluation procedures are of more interest to toxicologists and will be discussed in greater detail. It is important to note that the notification procedure for new chemicals is more detailed for nonpolymeric chemicals. Testing requirements for the various laws are summarized in Table 10.1. Historically, polymers have not been categorized as major health hazards for health and environmental effects, and thus were regulated with abbreviated notification procedures or an outright exemption for some or all polymers. Recently, more attention is being given to additives like plasticizers, which can have some biological effects. Many countries have adopted the OECD base set tests for new chemicals (OECD, 1981) and the OECD guidelines for Good Laboratory Practices (GLP, OECD, 1997b).

Typically, these laws only allow a fixed period of 45–90 days for review of notifications by the government agency. Some of these laws do not even require a formal *positive approval* from the

TABLE 10.1
Testing Requirements for New Chemicals Notifications for Major Countries[a]

Test Type	OECD Protocol	US[b]	EU	Japan	Canada	Australia
Mammalian Studies						
Acute oral	401	SR[c]	R	R	R	R
Acute dermal	402	NR	R	NR	R	R
Eye irritation	405	NR	R	NR	R	R
Skin irritation	404	NR	R	NR	R	R
Dermal sensitization	406	NR	R	R	R	R
Oral repeated dose	407	SR[c]	R	R[d]	R	R
Chronic toxicity	452	SR	NR	SR[e]	R	R
Reproductive toxicity	415	SR	FR	NR	NR	NR
Genotoxicity						
Bacterial mutagenicity (*in vitro*)	471	SR[c]	R	R	R	R
Mammalian cytogenetics (*in vitro*)	473	SR[c]	SR[c]	SR	SR	SR
Germ cell cytogenetics	478	NR	NR	NR	SR	R[e]
Mouse micronucleus[f]	474	SR[c]	SR	SR	SR	SR
Environmental						
Acute fish	203	SR[g]	R	R	R	R
Acute daphnia	202	SR[g]	R	NR	R	R
Acute algae	201	SR[g]	R	NR	R	R
Chronic daphnia	202	NR	NR	NR	NR	R
Biodegradation	301 or 302	NR	R	R[h]	R	R
Fish bioaccumulation	305	NR	NR	R[i]	NR	NR

[a] R = required in most instances; SR = sometimes required under certain circumstances; NR = not required in most instances; FR = future requirement likely.
[b] Although no formal testing requirements exist for new chemicals under TSCA, the EPA has authority to require virtually any test if serious questions of health and environmental safety arise. 40 CFR 720.50 requires that any available data on the health and environmental effects of the notified substances be submitted.
[c] Required when exposure-based concerns for human health are triggered.
[d] Japanese guidelines contain various additions to an OECD 407 such as additional tissues to be examined. Urinalysis and 14-day recovery groups for control and high dose groups also strongly recommended.
[e] Mouse micronucleus is usually allowed as a substitute for a germ cell cytogenetics assay.
[f] Mouse micronucleus may be required to resolve a positive *in vitro* cytogenetics result.
[g] Required when exposure-based concern for environmental effects are triggered. Check with the EPA for special customized protocols.
[h] Requires use of Japanese sludge sample and identification of metabolites of degradation.
[i] Japanese reviewers prefer *cold* chemical analysis methods as opposed to radiotracer studies.

government agency and the submitter is free to proceed with manufacture or marketing if there is no response from the agency regarding a notification.

United States 1976–2016

Congress enacted the Toxic Substances Control Act (TSCA) in 1976 (USC, 1976). The purpose of TSCA was to fill a regulatory gap by giving broad control to the Environmental Protection Agency (EPA) over industrial chemicals not regulated by other statutes. In the US, there was public concern over the risks from chemicals such as kepone, vinyl chloride, heavy metals and Polychlorinated

TABLE 10.2
Major Sections of TSCA

Section Number	Subject	40 CFR Reference
4	Chemical testing	Parts 700–799
	Good laboratory practices	Part 799
5	New chemicals	Part 720
	PMN exemptions	Part 723
5(a)	Significant new use rules	Part 721
6, 7	Existing chemicals control	Part 750
8(a)	Reporting concerning chemical use and manufacture	Parts 704, 712
8(b)	Inventory reporting rules	Part 710
8(c)	Adverse reactions (allegations) reporting	Part 717
8(d)	Health and safety data reporting	Part 716
8(e)	Substantial risk reporting	
12	Export rules	Part 707
13	Import rules	Part 707

Biphenyls (PCBs); also the President's Council on Environmental Quality (CEQ) identified a "high priority need for a program of testing and control of toxic substances" because the existing statutory mechanisms for protecting the environment against chemical hazards were neither cohesive nor adequate (CEQ, 1971).

Under TSCA, the EPA can impose wide-ranging requirements on importers and manufacturers of chemicals to test chemicals, to control the way chemicals are manufactured and used, and to report certain information and activities to the agency. TSCA is somewhat of a misnomer; the law gives authority to the EPA for all chemicals that are not regulated by other laws, such as pesticides and food additives. The term toxic is not even defined in TSCA or in EPA regulations.

The law is divided into a number of sections. Procedures that require pre-manufacturing clearances and other requirements for new chemicals are outlined in Section 5. Other sections deal with existing chemicals. Regulations promulgated by the EPA under TSCA are listed in Title 40 of the Code of Federal Regulations (CFR) in parts 700–799. The main sections of the law and corresponding parts of 40 CFR are listed in Table 10.2. Compared to its international counterparts, TSCA contains the most detailed reporting requirements on existing chemicals as well as specific provisions to require manufacturers, importers and, in some cases, processors of existing chemicals to conduct needed toxicology testing.

The EPA is divided into several different offices, each of which has responsibility for different laws that address different aspects of the environment: air pollution, water pollution, waste disposal, pesticides and toxic substances. Currently, the Office of Pollution Prevention and Toxics (OPPT) of the EPA enforces TSCA. The organization of these offices has changed from time to time (EPA, 1993a). There is little interchange between the offices or even divisions within an office that administer different laws. The scientists in the divisions of OPPT who are responsible for pesticides use many different tools and standards than the scientists who are responsible for industrial chemicals under TSCA.

Toxicology staff and regulatory professionals play a key role in the TSCA compliance efforts of a company that manufactures or processes industrial chemicals. This chapter will focus on those sections of TSCA that are usually the responsibility of toxicologists. TSCA compliance requires many activities that usually need the attention of regulatory affairs specialists and scientists with expertise in chemical nomenclature, manufacture, sales and marketing activities. These requirements will receive less attention in this chapter. The reader is referred to the text of the regulations and other information from the EPA for details.

A vital step in adhering to compliance is keeping up with new information on TSCA. Besides new regulations, the EPA frequently makes new policy statements and guidance documents available. A former key publication, the *Chemicals in Progress Bulletin* was consolidated into a revamped publication entitled *Chemicals in our Community*. The EPA publishes this quarterly and subscriptions are free. It contains summaries of regulatory and compliance activities related to TSCA. Over the last few years, accessibility to EPA guidance documents and summaries of EPA programs has improved dramatically with the introduction of the EPA's website, which is now the main source of updated information on TSCA.

The TSCA Chemical Substances Inventory was developed according to the procedures Section 8(b) and initially consisted of those substances in commerce in the US between January 1, 1975 and June 1, 1979. As new chemicals are reported to the EPA and commercialized, they are added to the TSCA Chemical Substances Inventory.

A new chemical or polymer is notified through an application process called a Premanufacturing Notice (PMN). The notification must be submitted on the prescribed PMN form, which calls for a complete chemical identity, impurities, use description, manufacturing locations and process descriptions, and worker, customer and environmental exposure data. Requirements for PMNs in the US differ from those in many other countries in that no specific toxicity testing is required to be conducted before notification. By regulation (40 CFR 720.50), however, all available toxicity data known to the notifier as well as any data related to health and environmental impact of the chemicals must be submitted. A detailed guideline for PMN submitters is available on the EPA website (EPA, 1997).

In order for the EPA to decide within the statutory 90-day review period without benefit of a standard data set, the EPA relies heavily on structure activity relationship (SAR) determinations on the chemical to judge whether it can be manufactured and used safely. The EPA develops structure activity relationships from known publicly available data and proprietary data submitted by other notifiers or reporters of information under other sections of TSCA (Wagner et al., 1995). This review is conducted under a very regimented procedure that is tightly scheduled in the 90-day review period as described in Figure 10.1. Over the last several years, the EPA has added several computer models for exposure modeling and for SAR determinations. The EPA has begun to hold workshops for scientists who work for regulated companies so that they can use the models to anticipate the results of the EPA review. The list of models currently used by the EPA is given in Table 10.3 (EPA, 1998), and details on how the exposure models are used are in the 1997 guidance document.

In cooperation with European regulators, the EPA participated in a joint study comparing their SAR projections against data submitted under the European notification scheme. A report is available that compares the results of the two approaches (EPA/EC, 1994). The EPA has used this study to help improve their SAR models.

The 1997 guidance describes 11 possible outcomes of PMN review. The most common outcome is an early *drop* from the review process. This occurs for about 80% of the PMNs. Further review exonerates the majority of the remaining PMNs from concern, and all these chemicals can be marketed without further controls. About 5% of the cases progress to *standard review*.

The EPA uses a variety of methods to control chemicals that make it to standard review. The EPA will sometimes issue a *letter of concern* to the submitter asking for some specific voluntary control in the way the chemical is manufactured or used. The EPA has a great deal of flexibility under Section 5(e) of TSCA to impose controls or require the submitter to submit further information. Commonly, additional testing data is required via a formal written agreement called a consent order with the submitter. Consent orders can be used to impose controls on manufacturing or use of the chemical substance. Depending on the need for notifying other possible manufacturers, the EPA may also issue a Significant New Use Rule (SNUR). In the rare instance that the chemical cannot be manufactured and used safely, the EPA can prohibit manufacture and sale under Section 5(f).

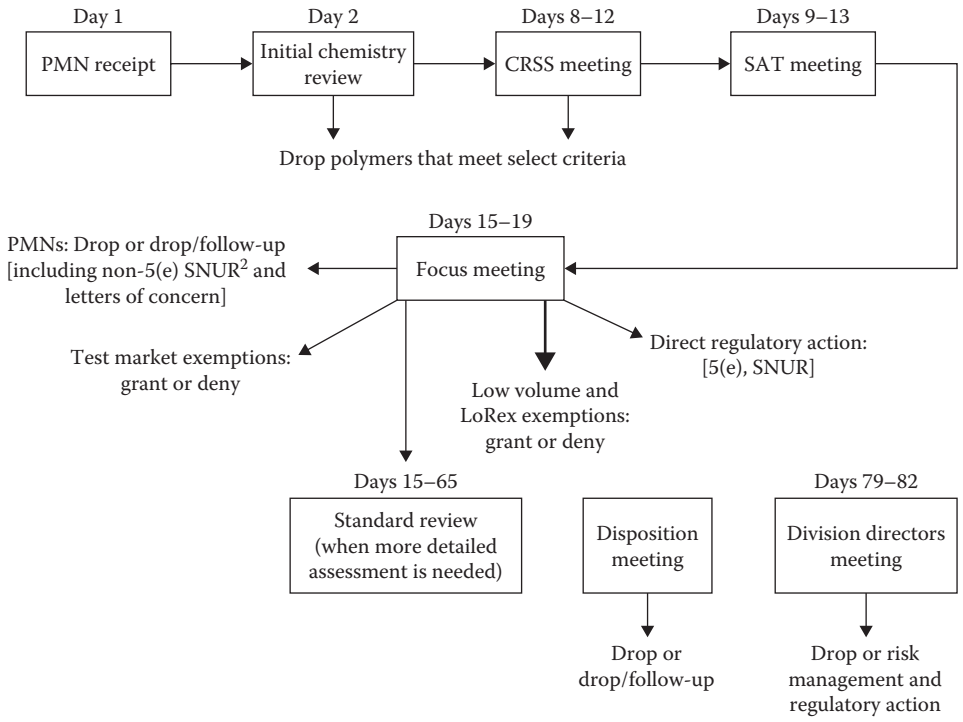

FIGURE 10.1 EPA/OPPT review process for PMNs on new chemicals.

TABLE 10.3
Models Used by Scientists at OPPT to Review Estimate Exposure, Environmental Fate and Hazards of Chemical Substances

Model	Predicts
Environmental Fate and Exposure Models	
KOWWIN	Octanol water partition coefficient (atom fragment method)
AOPWIN	Atmospheric half life
HENRYWIN	Henry's law constant (air/water partition coefficient)
MPBPWIN	Melting point, boiling point and vapor pressure
BIOWIN	Rate of biodegradation
PCKOCWIN	Soil and sediment adsorption
WSKOWIN	Octanol water partition coefficient and water solubility
HYDROWIN	Rate of hydrolysis
BCFWIN	Bioconcentration factor
WVOLWIN	Rate of volatilization from surface waters
STPWIN	Removal by waste water treatment plant
LEV3EPI	Fugacity, partitioning between soil and water
Hazard Modeling	
ECOSAR	Toxicity to aquatic species
ONCOLOGIC	Potential for carcinogenicity

TABLE 10.4
The EPA Exposure Based Criteria for PMNs. If Information in a PMN Indicates That the Production Volume Is Exceeded and One of the Following Criteria Are Met and There Is Insufficient Data on Similar Chemicals to Make a Judgment on Safety, the EPA may Require the Studies Indicated in Table 10.2

Exposure Parameter	TSCA 5(e) Exposure-Based Policy Criterion
Production volume	100,000 kg/year
Significant or substantial human exposure: high number of workers exposed	≥1,000 workers
Significant or substantial human exposure: acute worker exposure, inhalation	100 workers exposed to ≥10 mg/day
Significant or substantial human exposure: chronic worker exposure, inhalation	≥100 workers exposed to 1–10 mg/day for ≥100 days/year
Significant or substantial human exposure: chronic worker exposure, dermal	≥250 workers exposed by routine dermal contact for ≥100 days/year
Significant or substantial human exposure: consumer	Presence in consumer product where exposures are likely
Significant human exposure: ambient general population	≥70 mg/year exposure via drinking water, air, or groundwater
Substantial human exposure: ambient general population	≥10,000 kg/year release to environmental media
Substantial environmental release	≥1,000 kg/year total release to surface water calculated after wastewater treatment

The EPA has formalized many of the procedures for requiring test data or implementing SNURs after reviewing a notice. A *risk based* determination can be based on high probability of a suspected hazard. Notifiers can anticipate these hazards by reviewing the EPA's report on suspected health and environmental concerns of various chemical categories (EPA, 1993b). This report is periodically updated on the EPA's website.

The EPA introduced an *exposure based* program to prescribe testing when high human or environmental exposure of the notified chemical is coupled with lack of human health or environmental effects data, respectively (EPA, 1991a). The exposure criteria are listed in Table 10.4 and the testing requirements are listed in Table 10.1. The EPA implements the risk and exposure procedures in a manner that is difficult for notifiers to predict. Not every chemical that meets the exposure criteria is required to be tested. The EPA will not require testing if an adequate SAR determination is attainable. The lack of predictability of when the EPA will require testing is due to the complex nature of their SAR methods, and the fact that the EPA is privy to proprietary data submitted by other notifiers and reporters. Practitioners can learn to anticipate these requirements for particular chemical categories if their company reports on a series of similar chemicals over time.

The various offices and programs of the EPA are currently focusing more of their efforts to anticipate chemicals that exhibit environmental persistence and bioaccumulative and toxic properties (PBT chemicals). This is being done proactively to help prevent the proliferation of chemicals that may have properties similar to PCBs, poly brominated biphenyls (PBBs) and dioxins. The EPA has implemented a set of criteria to trigger testing for new chemicals that could have the properties of a PBT chemical (Federal Register, 1999a). Criteria for testing under this policy are listed in Table 10.5.

SNUR procedures are listed in 40 CFR Part 721, Subpart A. Subpart B lists scores of various boilerplate descriptions of conditions that the EPA typically uses to define significant new uses. Chemicals with SNURs are listed in Subpart E. These restrictions define the conditions under which the use of the chemical would be considered a significant new use as defined by

TABLE 10.5
New Chemicals Program PBT: Category Criteria and Process

	TSCA Section 5(e) Action	
	5(e) Order Pending Testing Significant New Use Rule (SNUR)[a]	5(e) Ban Pending Testing[b]
Persistence (transformation half-life)	>2 months	>6 months
Bioaccumulation (fish BCF or BAF)[c]	>1,000	>5,000
Toxicity	Develop toxicity data where necessary[d]	Develop toxicity data where necessary[d]

[a] Exposure/release controls included in order; testing required.
[b] Deny commercialization; testing results may justify removing chemical from *high risk concern*.
[c] Chemicals must also meet criteria for MW (<1,000) and cross-sectional diameter (<20A, or $<20 \times 10^{-8}$ cm).
[d] Based upon various factors, including concerns for persistence, bioaccumulation, other physical/chemical factors, and toxicity based on existing data.

the statute. The major categories of SNUR restrictions include occupational exposure controls, pollution prevention measures and marketing restrictions. If a company wishes to manufacture or use a chemical as defined in the SNUR, a Significant New Use Notification (SNUN) would be required to be submitted. This is done using the same form for PMNs. Practitioners should be aware that a significant amount of new data is normally required by the EPA to convince them that the new use is safe.

Once a consent order is signed, or the 90-day review period has expired without the EPA contacting the notifier about extending the review period, the chemical can be imported or manufactured for commercial use. Within 30 days of its first manufacture or import, notifiers must submit a Notice of Commencement to the EPA.

Polymers can be notified on the same PMN form. Manufacturers of polymers that meet the structural and compositional exemption criteria in 40 CFR 723.250 can elect to submit annual reports on exempt polymers rather than notifying them individually.

Due to the flexible nature of TSCA as a *gap-filling* statute, the EPA has developed detailed procedures for the regulation of new products of biotechnology for industrial use (Federal Register, 1997).

TOXIC SUBSTANCES CONTROL ACT UPDATE IN 2016

On June 22, 2016, President Obama signed the Frank R. Lautenberg Chemical Safety for the twenty-first Century Act. The effort represents several years of bi-partisan negotiation to amend and reform the Toxic Substances Control Act from the late 1970s. The new law has major impacts on how the government will review not just new, but existing inventory chemicals, as well as how industry and non-governmental organizations will interact. The EPA has created a website for the program and updates it here: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/frank-r-lautenberg-chemical-safety-21st-century-act.

The new law will require the EPA to systematically review the safety of commercial chemicals, excluding those regulated as food, drugs, or pesticides. The goal is to ensure that no chemical in commerce poses an unreasonable risk the human health or the environment. The agency has had little real regulatory action directly on commercial substances since 1991, when a federal appeals court denied the EPA the power to ban asbestos products as cancerous. The agency also was limited to reviewing new chemicals versus the existing inventory for practical purposes after the 1991

decision. The agency will start conducting its new work by conducting risk reviews of at least 10 chemicals from a priority list of 90 chemicals.

Another major change in the law is in how trade secrets are managed. The Lautenberg act requires chemical manufacturers/importers to provide evidence to support the need or justify a confidential claim (not otherwise in commerce, proprietary). Claims will expire after 10 years unless re-asserted. Under the old law, Confidential Business Information (CBI) claims would never expire.

On the testing side, the new law also aims to reduce the use of laboratory animal testing. The mandate is that the EPA must opt, whenever practical and justified, to use alternatives to animal testing on chemical toxicity for studies done with vertebrates. EPA will have to identify these methods that it will consider reliable and relevant enough to replace animal tests to make regulatory and risk assessment decisions.

The last, but not least, important update is how the new federal law manages chemical regulations by the states, a topic which stalled passage of the bill until acceptable compromise was reached. Under the compromise agreement, states, which have bans on chemicals in commerce, are allowed to retain bans based on legislation that was passed before April 22, 2016. If any future actions of the EPA determine that the chemical does not pose unreasonable health to human or environmental health, then the EPA forbids the states to act on that law (hence preemption, or federal over state power). However, it is expected that the EPA will take a long time to review the existing or priority chemicals in the inventory, and states are free to pass legislation on any chemical that has not been reviewed at the EPA or released a determination on its risk to human and environmental health.

Recent activity based on the new law has included legislative action focusing on some *priority* substances, such as neonicotinoids pesticides, which are of special interest due to potential risks to bees. Other priority substances of interest include solvents used in painting and coatings, including *N*-methylprrolidine, methylene chloride, (which is already proposed for ban), and trichloroethylene. Another category of priority substances includes a category of flame retardants, with tris(2-chloroethyl) phosphate (TCEP) being the one of most note. The last category are asbestos products, stemming from the fact that, even though the court system overturned the EPA's previous ban on the products, the multitude of lawsuits from liability claims of exposed individuals who developed cancer or asbestosis has been the economic driver for most commercial manufacturers of asbestos to take their products of the market.

In summary, regulatory stakeholders should expect a lot of planning, rulemaking, and implementation of the new law at the EPA, new chemical legislation at state level, and new chemical testing in the industry consortia to deal with the new regulatory frameworks of the Lautenberg act. To date, no methods to replace animal tests have been identified or recommended for risk assessment and regulatory decision making.

Europe Pre-Reach

The Dangerous Substances Directive (DSD) became effective in 1967 (European Commission, 1967; 67/548/EEC). Many revisions have taken place since then in the form of eight amendments and 25 adaptations. Unlike the laws in the US, this directive has a more comprehensive authority to implement oversight on not only the manufacture and control of risks of new and existing chemicals, but also to mandate labeling and hazard communication requirements for both industrial chemicals and a wide range of consumer products other than drugs, food additives and pesticides. Because the law is administered by agencies of all the member states of the EU, practitioners may encounter variations in the way the law is interpreted and administered in the individual member countries.

The DSD, Directive 67/548/EC (European Commission, 1967) provides the basis for the harmonized classification of packaging and labeling of chemicals in the EU. In 1979, the Council

of Ministers of the European Community adopted the 6th Amendment to the DSD, or Directive 79/831/EC (European Commission, 1979), which introduced a notification system and mandatory testing requirements for new chemicals in addition to requirements for classification and labeling of dangerous chemicals. All member states had two years to adopt these harmonized procedures. This 6th amendment was superseded by the 7th amendment, Directive 92/32/EC (European Commission, 1992), which had to be implemented by October 31, 1993. The 7th amendment defines the current requirements for introduction of new chemicals to markets in the EU.

A new chemical is defined as one that is not on the European Inventory of Existing Chemical Substances (EINECS). EINECS was compiled from industry nomination of chemicals that were placed on the EU market in the 10-year period between January 1, 1971 and September 18, 1981. It is a closed list to which no additions are permitted. Polymers are *considered as notified* and are exempt from notification provided they do not contain more than 2% of a new monomer that is not on EINECS.

Once notified, new chemicals are listed on the ELINCS. ELINCS chemicals are identified by their trade names until the substance is added to Annex 1 of the DSD. This lists the chemical substances that have mandatory hazard classifications under the DSD. Listing in ELINCS does not mean that the substance no longer has notification requirements. A notification is required from each new manufacturer of the chemical although data sharing with a previous notifier is encouraged.

The notification requirements for a new chemical substance are laid down in several annexes to the Directive. Annex VIIA is a full notification for chemicals placed on the market in quantities greater than 1 metric ton/year. If less than 1 metric ton/year, consult Annexes VIIB or C and, if greater than 10 metric tons/year, consult Annex VIII, Levels 1 and 2. If a polymer needs to be notified then consult Annex VIID. In any case, there is an annex that will describe the appropriate situation and the corresponding notification requirements. A typical chemical notification dossier, Annex VIIA, (for a chemical placed on the market at 1–10 metric tons/year), contains spectral, physiochemical, toxicological, and ecotoxicological data, together with a summary of information that must be submitted as an electronic file in Standard Notification Information Format (SNIF). Table 10.1 indicates the tests required for this type of a notification.

The EU was the first to adopt the base set of tests recommended by the OECD for screening for the hazards of new chemicals (OECD, 1981). All tests are to be performed by current OECD test protocols and the laboratory performing the tests must abide by GLP. These details are all spelled out in Annex V. Again, since national agencies in the various member states are charged with reviewing the notifications, subtle differences in requirements, preferences, and review predisposition become evident with repeated notification experience. Data from laboratories around the world that meet GLP requirements are generally accepted although subtle nuances between national agencies are observed. For instance, in many member states, dermal sensitization by the maximization protocol is preferred over the topical assay, even though both are acceptable alternatives in an OECD 406 study (OECD, 1993).

In addition, the notifier supplies a classification and labeling proposal for the substance and a Material Safety Data Sheet (MSDS). Council Regulation No. 93/67 (European Commission, 1993a) mandates a risk assessment approach in the review of new chemicals. The notifier may provide a preliminary risk assessment for the substance, although the ultimate responsibility of the risk assessment as required by the 7th Amendment rests with the competent authority. Possible outcomes of the risk assessment process are given in Figure 10.2. More details on the risk assessment approach can be found in the extensive technical guidance document (European Commission, 1996).

Notifiers of new chemicals must report annual production or import volume each year. Once an annual volume or cumulative volume exceeds a trigger volume, additional testing must be negotiated with the authorities. The tests that must be considered are listed in Schedule 3 of Annex VIII.

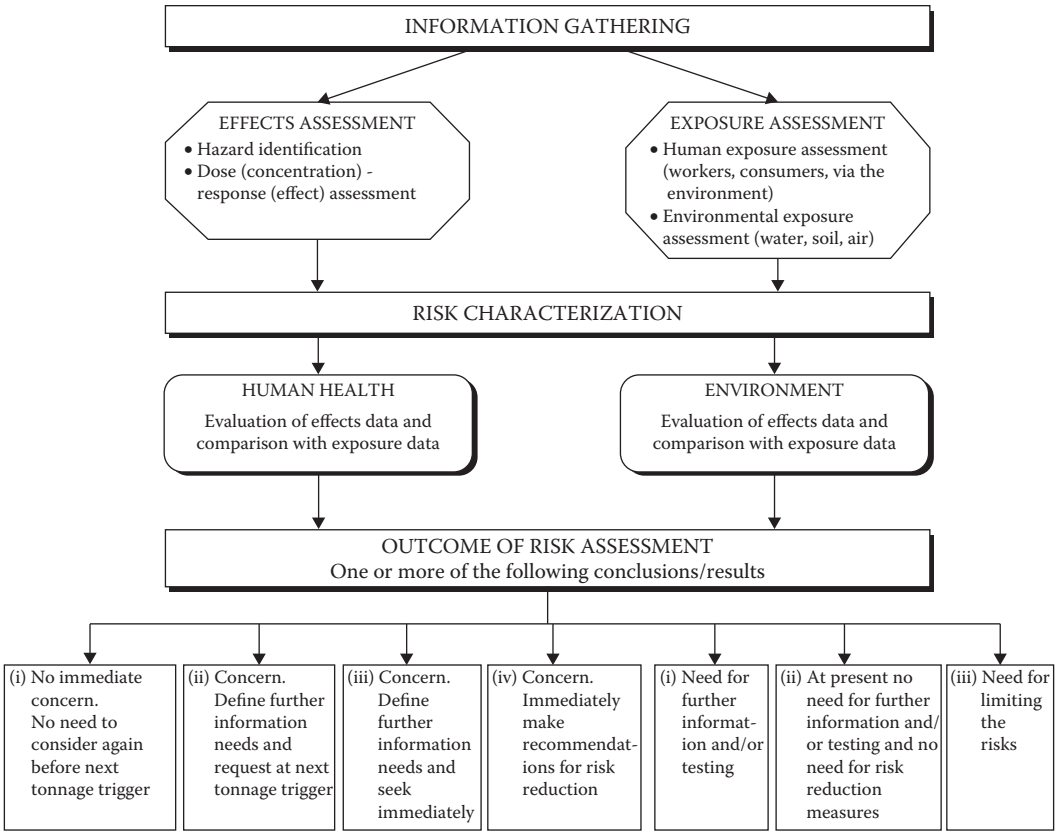

FIGURE 10.2 A schematic outline of the major steps and possible outcomes of the EU risk assessments for new and existing chemicals under adaptation EC/793/93 of the Dangerous Substances Directive.

EUROPE POST-REACH

REACH stands for Registration, Evaluation, Authorization and Restriction of Chemicals, and its enforcement began on June 1st, 2007. REACH places the burden of proof on companies to collect and evaluate hazards, and then submit them to the government for review. This form of legislation was a major shift from the North American approach where the burden of deciding what tests to use and decisions needed to be made regarding those tests fell onto the government. To comply with the regulation, companies must identify and manage the risks linked to the substances they manufacture and market in the EU, prioritized by hazard. An example of the hazard-leading approach over risk is that the European Chemicals Agency (ECHA) maintains a list of Substances of Very High Concern (SVHCs). They must demonstrate how the substance can be safely used, include exposure scenarios for chemicals that have hazards that must be managed, and communicate the risk management measures to the users, both occupational and to the larger community. If the risks cannot be managed, authorities can restrict the use of substances in different ways.

REACH establishes procedures for collecting and assessing information on the properties and hazards of substances. Companies often organize into consortia with the title of substance information exchange forums, or (SIEFs). In SIEFs, companies either share data or offer to sell data rights to other companies depending on the competitive position. Companies need to register their substances within the given deadlines based on the annual metric tons of production or import volume. To do this they need to work together with other companies who are registering the same substance. ECHA receives and evaluates individual registrations for their compliance, and the EU

Member States evaluate selected substances to clarify initial concerns for human health or for the environment, that organize these into Community Rolling Action Plans (CoRAP). All of the chemicals listed as an SVHC, as described earlier, will undergo CoRAP reviews or are already under review. It is likely that the highest risk chemicals will undergo procedures of restriction and high economic cost and requirements to justify authorizing or continued use of the chemical in the marketplace. Authorities and ECHA's scientific committees assess whether the risks of substances can be managed.

Authorities can ban hazardous substances if their risks are unmanageable. They can also decide to restrict a use or make it subject to a prior authorization.

UK-EU-BREXIT UPDATE

In 2016, the citizens of the United Kingdom voted to leave the European Union. For now, the country is still a participant in the EU REACH regulations and may continue through the final deadline for chemical registrations in 2018 unless separation is completed in an expedited time frame. As it is likely that the United Kingdom will continue to be a part of the European Economic Alliance outside of the EU, participation in the compliance requirements as administered by the ECHA is likely.

Japan

Japanese laws and regulations present much difficulty to companies based in Western nations. Japanese requirements for the control of industrial chemicals have many important differences from the requirements in Europe and the US. The law that affects new chemical notification is the law concerning Examination and Regulation of the Manufacture, and so on, of Chemical Substances and is administered by the Ministry of International Trade and Industry (MITI) and the Ministry of Health and Welfare (MHW). The law was established in 1973 to prevent environmental pollution and hazards to human health by chemical substances used for various purposes. The impetus for its enactment was the problem of environmental pollution caused by PCB in the late 1960s. New chemicals must also be notified under the Industry Safety and Health Law of 1977. This law is administered by the Ministry of Labor (MOL) and aims to protect health in the workplace. The MOL is primarily concerned with the prevention of occupational cancer.

The best source of information on Japanese laws and regulations in the English language is the *Handbook of Existing & New Chemical Substances* (The Chemical Daily Co, Ltd., 1999). The handbook contains the full text of the laws, reporting forms, testing guidelines, review criteria, as well as the lists of Existing Chemical Substances, New Chemical Substances and Specified Chemical Substances.

Canada

The Canadian Environmental Protection Act (CEPA) was passed in 1988 and significantly amended in 1999. The law is a comprehensive environmental statute rather than just a simple chemical control law. The law includes many provisions that are like TSCA, but also contains some requirements similar to the DSD. CEPA established two chemical inventories of called the Domestic Substances List (DSL) and the Non-Domestic Substance List (NDSL). The law contains authority to regulate both new and existing chemicals. The act also names eleven prohibited substances. In the recent amendment to the law, the term toxic was defined as

> a substance... entering the environment or (that) may enter the environment in a quantity or concentration having or that may have an immediate or long-term harmful effect on the environment, or its biological diversity, or on its human life or health....

The chemical control provisions of CEPA are primarily administered by Environment Canada with help from Health Canada. Environment Canada has a website, publishes guidelines for compliance, and holds periodic educational workshops. The reader can find more information at the hyperlinked websites. Health Canada Decision Making Framework: http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php. Environment Canada Assessment of Substances CEPA 1999 http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=EE479482-1&wsdoc=16C8586D-F376-5225-C45C-6EAC80B5E0B9.

Australia

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) was established in 1989 with the passage of the Industrial Chemicals Notification and Assessment Act to protect the public and the environment from the harmful effects of industrial chemicals. NICNAS is administered by three agencies, the National Occupational Health and Safety Commission (NOHSC, also known as Worksafe Australia), Environment Australia and the Therapeutic Goods Administration of the Department of Health and Family Services. NOHSC has a website and a number of guidelines and publications on assessment activities are available. Currently, the regulations are being updated by the Council of Australian Governments (COAG) Chemical Reforms.

New Zealand

Risk Assessment Frameworks are published and available under the Department of Food Safety and the New Zealand Environmental Protection Authority. The reader is encouraged to visit the site for more information. The New Zealand Environmental Protection Agency has its own historical classification system, including the Chemical Classification and Information Database (CCID) that maintain classifications according to Hazardous Substances and New Organisms (HSNO) regulations. Chemicals allowed in New Zealand are managed on the New Zealand Inventory of Chemicals (NZIoC).

Korea

The Toxic Chemicals Control Act (TCCA) was enacted on August 1, 1990 to control chemical substances that are hazardous to human health or the environment. The law is administered by the Korean Ministry of the Environment (MOE).

The MOE has established a registration and evaluation program of chemical substances very similar to the European REACH regulations. It is so similar, that it is called K-REACH (Korea-REACH). The regulations apply to any company that will manufacture or import any chemical subject to registration at 1 ton or greater on an annual basis. The registration process will include hazard evaluation and risk assessment of the chemical within one to two years of registration. For more information visit the link provided here: http://eng.me.go.kr/eng/web/index.do?menuId=167.

Philippines

The Philippines Chemical Control Law is the 1990 Toxic Substances and Hazardous Waste Control Act (the Philippines Republic Act 6969), which covers import, manufacture, processing, handling, storage, transport, sale, distribution, use, and disposal of chemical substances and mixtures. The Act is administered by the Department of Environment and Natural Resources (DENR). DENR has a website, however, as of this writing, it has no information on the chemical control law.

Japan

The Chemical Substances Control Law was established in 1973 to prevent environmental pollution and hazards to human health by chemical substances. The impetus for its enactment was the

problem of environmental pollution caused by PCBs in the late 1960s. It provides for a classification of new chemical substances that have similar properties to PCB (low biodegradability, high bioaccumulation, and chronic toxicity) as Class I Specified Chemical Substances and, in fact, virtually prohibits the manufacture and import of such substances.

The law was amended in 1986 and introduced the system for assigning Designated Chemical Substances and Class II Specified Chemical Substances. This originated out of the necessity to regulate substances having the properties of low bioaccumulation, but low biodegradability and chronic toxicity, depending on the degree of persistence in the environment.

The main objective of the law is to protect humans from exposure to dangerous substances in the environment and especially from dangerous substances that could enter the food chain. Their approach to new chemical control is somewhat different from the rest of the world. They place great emphasis on biodegradation and bioaccumulation. The biodegradation test is required to identify any unique metabolites resulting from biological action. Depending on the results of the biodegradation study, ecotoxicity and toxicity studies may be required on the environmental degradants and not necessarily on the parent compound. For this reason, as well as other possible nuances in interpretation of the results, practitioners usually perform the required tests in a stepwise fashion and discuss the results with scientists from the Japanese agencies before going on to the next test. The basic testing requirements are outlined in Table 10.1, but the reader should take notice of the many footnotes in the table.

Although the tests for MITI/MHW/MOL notifications are based on OECD test methods, one should consult the Japanese test guidelines because often the tests are more stringent and may require, for example, unique Japanese test media or species. In practice, most practitioners have found that a greater probability of a successful notification is obtained when the environmental tests are done by Japanese laboratories. Data from laboratories outside of Japan are usually accepted for health effects studies if the laboratory has successfully undergone the Japanese certification process for GLP.

The test data is reviewed by MITI and MHW. Separate notification must be made to the MOL. Their review focuses on the protection of workers from new chemicals and they are particularly concerned about the introduction of new carcinogens. The only data required to be submitted to the MOL is a bacterial mutagenicity test.

If a notified chemical is biodegradable, it is classified as a *safe* chemical and no further testing is necessary. However, very few synthetic chemicals meet the biodegradation criteria. Next the substance or its nonbiodegradable metabolite is assessed for bioaccumulation. If the material is not bioaccumulative, it undergoes a set of toxicity studies: a 28-day subacute oral toxicity in rat, Ames mutagenicity and *in vitro* chromosome aberration tests. If the material does bioaccumulate, then a more detailed set of toxicity testing is required. This entails a great many discussions with MITI and could become an expensive and long notification process. In the end, these substances may be deemed *safe* or may become Class I or II Specified Chemical Substances or Designated Chemical Substances. In the Japanese notification process, consultations with MITI are expected and advisable. Rarely can a notifier be successful by simply submitting test results and a form to the Japanese authorities without prior consultation. The major decision points in the review of submitted data are listed in Figure 10.3.

All notified chemicals are eventually added to the list of new substances. Initially, only the notifier can manufacture or import this substance until the substance is published in the Official Gazette; this usually occurs 1–3 years after the new chemical dossier is examined and approved. The lists of existing and new chemical substances do not use CAS nomenclature but rather consists of some 20,000 entries which are often more generically described rather than listing specific substances. The generic listings make it possible that an entirely new chemical may be adequately described by a preexisting listing so that no notification would be required. The lists are difficult to use, and practitioners should consult the Explanation and Examples of Classification Based on Chemicals Structure (The Chemical Daily Co, Ltd., 1999).

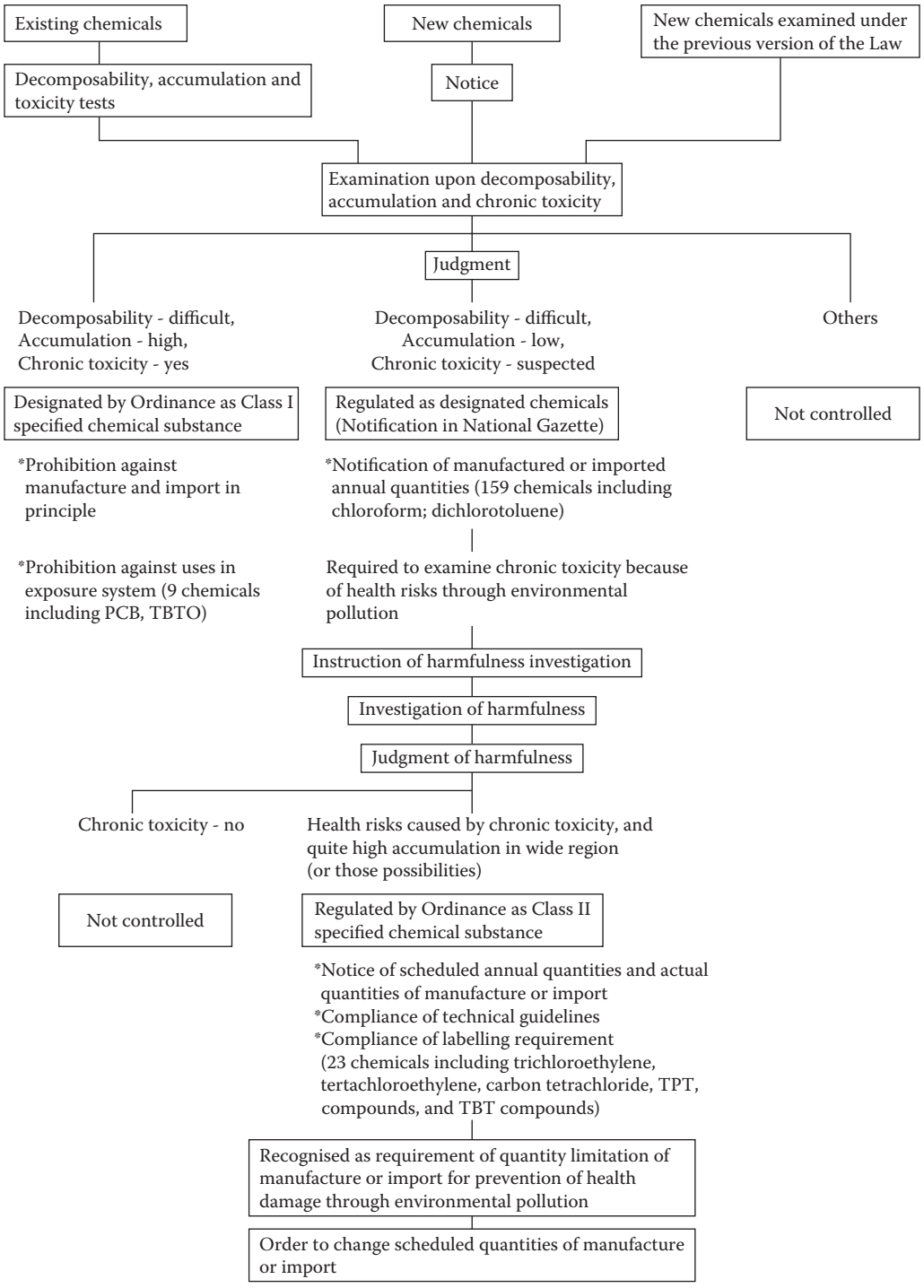

FIGURE 10.3 A flowchart indicating data needs and logic of assessments and possible outcomes under the Japanese system administered by MITI and MHW (OECD, 1997). Systematic chart of the law concerning examination and regulation of manufacture, and so on, of chemical substances (those in parentheses designated as of November 1995).

There is also a polymer notification scheme. The polymer is evaluated for photo, thermal and hydrolytic stability, solubility in water under acidic and alkaline conditions, solubility in various solvents, structural characteristics; molecular weight distribution and proportion of oligomers. If it passes this evaluation it is deemed *safe*, but if not, it is considered nonpolymeric and must be fully tested. In summary, chemical management and risk assessment in Japan is managed by the National Institute of Technology and Evaluation, administered under the title of Chemical Risk Information Platform, it can be accessed at this site: http://www.safe.nite.go.jp/english/db.html.

Canada

CEPA is the primary legislative instrument in Canada for environmental protection. Part II of the Act concerns the introduction, by import or manufacture, of new substances into Canada through a requirement for a pre-import or pre-manufacture notification and assessment. The legislation came into force in July 1994. A number of procedural inefficiencies were addressed by the CEPA amendment of 1999.

The Canadian DSL is their inventory of chemicals that were in commercial use in Canada between January 1, 1984 and December 31, 1986. As new chemicals are notified they are placed on the DSL. Canada also created an Non-Domestic Substances List (NDSL). The original NDSL consisted of chemicals on the 1985 TSCA inventory that were not on the DSL. Chemicals listed on the NDSL could be placed on the DSL with reduced notification requirements.

The Department of the Environment (Environment Canada) and the Department of National Health and Welfare (Health Canada) assess new chemical notifications. The assessment will result in:

1. A determination that the substance is not suspected of being toxic; or
2. A suspicion that the substance is toxic, which may require: (1) controls on, or prohibition of, import and manufacture or (2) prohibition pending submission and assessment of additional information; or
3. Limiting the purpose for which a substance may be used to permit the waiver of information requirements.

The notification requirements are tiered in a unique fashion under the Canadian notification system. The information requirements depend on the chemical class (e.g., polymer, chemical, biotechnology product), volume of import or manufacture and proposed use (e.g., research and development, etc.). The Guidelines for the Notification and Testing of New Substances: Chemical and Polymers (Environment Canada, 1993) is a critical reference tool for Canadian notifications. The appropriate flow charts and the appropriate notification schedule in the guidelines must be ascertained before filing a notification. The full data package for a nonpolymeric chemical (Schedule III), when required, is very similar to a EU test package based on OECD protocols done under GLP procedures (Table 10.1). However, data can be supplied in three forms: actual test data, surrogate data (data either calculated or based on structural analogs), or requests for waivers of information requirements if testing is not possible or relevant due to the properties of the chemical. Once a schedule is filed and reviewed, the quantity of chemical manufactured or imported into Canada is tracked until the next schedule is filed. Eventually an ultimate schedule is filed and once the trigger volume is exceeded, the material is listed on the DSL.

Australia

In Australia, an industrial chemical is defined as one that is not an agricultural or veterinary chemical, a therapeutic good, or a food or food additive. It is interesting to note, that unlike the status in the US, chemicals used in cosmetics are considered industrial chemicals.

The chemical inventory was created from the chemicals that were commercially in use in Australia from December 1, 1977 to July 16, 1990. New chemicals are added to the inventory 5 years after a notification is approved. During the 5-year interim period, the notifier alone has the right to manufacture or import the new chemical.

There are notification requirements for chemicals and polymers. Assessments should be completed in 90 days. Manufacture cannot begin until an assessment certification is given. It seems to take several weeks to months to obtain the assessment certificate before manufacture or import is allowed. A Notice of Commencement is required upon first manufacture or import.

The notification for a chemical requires an information set very similar to that of the EU. All the tests are required to be performed according to OECD guidelines under GLP procedures. See Table 10.1 for details. The notification scheme also provides for a certain amount of flexibility in the data requirements. A waiver may be requested (for a fee) if the test required can be shown to be irrelevant, unnecessary or economically prohibitive. As with most notification schemes in other countries, there are reduced notifications or exemptions for small volumes of chemicals, site-limited chemicals and substances used in various quantities for research and development. A Handbook for Notifiers can be ordered through the NOHSC website (NICNAS, 1995).

Polymers are notified as new synthetic polymers with number-average molecular weights of less than 1,000, as new synthetic polymers with number-average molecular weights of more than 1,000 or as polymers of low concern. If the polymer molecular weight is under 1,000, then the notification resembles a chemical notification. The other polymer notifications do not require toxicity tests but do require characterization for molecular weight distribution, residual monomers, impurities and stability.

India

India has numerous chemical legislations and has also received global attention on chemical risk management due to the Bhopal Gas incident in 1984. Laws regulating chemicals include the Environment Act of 1986, Hazardous Chemical Rules Act of 2000, and Chemical Accidents Amendment of 1996. Currently, none of the governing ministries have managed databases or inventories that are accessible online.

Indonesia

In Indonesia, chemical regulations are managed by the Ministry of Environment; their focus appears to be on hazard management. The website for the department is http://www.menlh.go.id/.

China

There are several inventories of chemicals regulated in China. A searchable database is maintained at this website: http://cciss.cirs-group.com/.

In 2011, the Chinese Government published Decree 591 *Regulations on Safe Management of Hazardous Chemicals in China*. It is a complex piece of legislation that includes multiple governing bodies. The legislation covers the Hazard Communication (GHS) requirement, New Chemicals and Dangerous Goods, Food Safety, Cosmetics, Occupational Health, Plastics and Plasticizers, and Coatings. Chemicals will have to be registered in a *China REACH* style of legislation. Legislative Authority experts are centered at the Chemical Registration Center (CRC) of the Ministry of Environmental Protection (MEP) and the State Administration of Work Safety (SAWS) of the National Registration Center for Chemicals. An English translation of the entire regulation is available at this website: http://www.cirs-reach.com/China_Chemical_Regulation/Regulations_on_Safe_Management_of_Hazardous_Chemicals_2011_English_Translation.html.

Korea

The Korean TCCA became effective on February 8, 1991. It has been modified several times since and this has significantly simplified and streamlined the import and notification procedures. The Korean MOE administers the law.

The original Korean Existing Chemical Inventory included chemical substances manufactured or imported into Korea prior to February 8, 1991. All new chemical substances must be reported to the MOE at least 90 days before the first manufacture or import. The notification information includes technical and commercial information and some details on use and disposal. There are required studies on acute toxicity in rats or mice, mutagenicity studies (Ames and chromosomal aberration), and an *in vivo* mouse micronucleus test to confirm mutagenic potential if either of the mutagenic studies are positive. A biodegradation study, review of hydrolysis, photolysis and physical and chemical properties indicating persistence, and a review of bioaccumulation potential are required. These studies may be from the published literature or unpublished studies according to OECD or based on other acceptable protocols on the exact chemical substance or on an acceptable surrogate substance. An abstract in Korean is required for all foreign language test reports. The notification requirements are reduced for substances that are reported on two foreign inventories before 1991. The usual technical and commercial use and disposal information is required; but only an acute toxicity and Ames test are required.

The notification requirements for polymers (as defined by OECD) are simplified. A determination of number average molecular weight, weight per cent of residual monomers and oligomers with molecular weights below 1,000, certain physical properties (i.e., melting point, solubility in common solvents), as well as information on intended use and some manufacturing details are required.

In June 2013, The Korean Ministry of Environment has established a registration, evaluation program of chemical substances very similar to the European REACH regulations. It is so similar, that it is called K-REACH (Korea-REACH). The regulations apply to any company that will manufacture or import any chemical subject to registration at 1 ton or greater on an annual basis. The registration process will include hazard evaluation and risk assessment of the chemical within one to two years of registration. For more information visit the link provided here: http://eng.me.go.kr/eng/web/index.do?menuId=167.

Philippines

Title II of the Toxic Substances, Hazardous Waste and Nuclear Waste Control Act, deals with toxic substances. DENR is charged with protecting the public health and the environment from unreasonable risks posed by these substances.

DENR compiles, maintains and updates an inventory of chemical substances known as the Philippines Inventory of Chemicals and Chemical Substances (PICCS). The PICCS is composed of those chemicals manufactured, used or imported in the Philippines prior to December 31, 1993. As new chemicals are notified and reviewed, they are eventually added to the PICCS inventory. The PICCS is updated once every five years. During a 5-year interim period, only the notifier of the chemical may sell commercially.

Manufacturers and importers of new chemicals are required to notify the DENR of their intent to manufacture or import the new chemical. The DENR is responsible for assessing the potential risk posed to the public and health and the environment by the new chemical substance. This notification requires the submission of a Pre-Manufacturing and Pre-Importation Notification (PMPIN) form.

There are two kinds of PMPIN forms. The abbreviated form is used when a new chemical is in commerce with no controls in a country with a similar review process as the Philippines, and when the notifier believes there is sufficient information that clearly exhibits that the chemical will not pose an unreasonable risk. The instructions for the form call for a short description of

potential effects of the chemical. All available toxicological and environmental information should be addressed. Depending on the nature of the chemical, a good quality material safety data sheet may be an acceptable summary. If DENR is not satisfied with the first submission, they may require more comprehensive information on a more detailed PMPIN form including additional testing if they determine insufficient information has been submitted to assess the safety of the chemical.

Once DENR reviews the information and determines that the chemical will not pose an unreasonable risk, it will issue a clearance to import or manufacture the new chemical. A Notice of Commencing Import and Manufacture is required upon first import or manufacture.

Experience with the Philippine notification system is limited. PMPINS have been submitted to the Philippines since 1994 but DENR has only recently (mid-1999) appointed staff to review notifications. Little experience has been reported in the industry about the adequacy of the data submitted for these new chemicals and how they are being reviewed by the agency. There is little additional guidance available on the notification of chemicals and polymers in the Philippines.

The Philippines also has an Inventory of Chemicals and Chemical Substances (PICCS), which is administered by the Environmental Management Bureau.

Vietnam

Vietnam has been developing and updating chemical regulation laws over the past few years. In 2011, Decree No. 26/2011/ND-CP was passed that includes inventory lists and chemicals that are limited in production and trade conditions. The lists also include chemicals subject to declaration and toxic chemicals that require control slips for purchase. Decree No. 108/2008/ND-CP contains a list of banned chemicals. The government website for chemical management is located here: http://cuchoachat.gov.vn/Trangchủ.aspx.

International Harmonization

The OECD has been active in developing consensus on several processes associated with chemical regulation. Their recommendations for the mutual acceptance of data (OECD, 1981) for a minimum data set for the assessment of a new chemical (OECD, 1982) were published almost two decades ago. They have also published internationally recognized standards for GLPs (OECD, 1997b) and guidelines for health and environmental testing (OECD, 1993).

Their more recent activities have arisen from the United Nations Conference on Environment and Development held in Rio de Janeiro in June 1992. Agenda 21 from this conference describes a comprehensive program in the areas of environmental protection, climate change and sustainable development. Chapter 19 of Agenda 21 addresses the management of toxic chemicals. OECD activities have been directed to the development of recommendations for chemical management systems that are sound and globally harmonized.

The OECD held a conference in 1996 to explore means to increase international cooperation among the existing authorities that review new chemical notifications by these various laws. As a first step, this conference discussed means of sharing data among government agencies obtained from notifications for new chemicals. The background information in the report of the conference is a good source of information for the practitioner seeking more details of the various review and administrative processes under each law (OECD, 1997a). The conference identified potential common ground and goals of the regulatory systems of the various countries and possible means to share data. The US and Canada are sharing assessments under a pilot program called the Four Corners Agreement.

Harmonization of the notifications in these countries would take statutory changes by the legislative bodies of these countries. This would certainly take a long time to accomplish. New laws from other countries add to an already complex situation. Hopefully, any country contemplating instituting a new chemical control law will consider the guidance from OECD to avoid adding any more confusion.

WORLD HEALTH ORGANIZATION–INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

On an international level of cooperation, the World Health Organization (WHO) has an International Programme on Chemical Safety (IPCS). For developing nations without a risk assessment program, the IPCS will help establish standards in that country. There are several focus areas of the World Health Organization, including the Health Impacts of Chemicals, with a focus on chemicals of major public health concern. They also provide resources on assessment and classification.

THE UNITED NATIONS

The United Nations also has a working committee on the Strategic Approach to International Chemicals Management (SAICM). Similar to the World Health IPCS program, the goal of SAICM is to develop international guidance and standards on the management of chemicals.

REQUIREMENTS FOR EXISTING CHEMICALS

United States

Chemical Testing Requirements

The EPA has many options under TSCA to assess and control the risks of existing chemicals. Under Section 4 of TSCA, the EPA can require manufacturers and importers of chemical substances to conduct health and environmental testing under certain criteria listed in Section 4(a) of TSCA. The exact legal interpretation of these criteria has been somewhat controversial, but basically testing can be required when the EPA determines that an unreasonable risk may exist from current uses (hazard finding) or if there is substantial human or environmental exposure (exposure finding). Although Congress realized that new information could become known which would make further testing desirable and prudent, it did not give the EPA the authority to require testing without good cause.

The procedure for developing test rules is shown in Figure 10.4. Section 4 established the Interagency Testing Committee (ITC), an independent expert panel made up of scientists from various regulatory and research agencies. The law specifies that the ITC should issue a report annually to designate chemicals that would appear to be candidates for test rules, based on statutory criteria. New toxicology data and exposure patterns are taken into account. The EPA studies the recommendation and obtains additional information from industry through Section 8: reporting rules (Walker, 1993).

The EPA further investigates the production, use, and existing data on the chemicals listed by the ITC. If sufficient reason appears to exist to support a test rule, the EPA publishes a notice of proposed rulemaking, which discusses the need for the test rule and a list of tests that are thought to be needed to more fully evaluate the risks of the chemical. The manufacturers and importers can challenge the basis for the rule and dispute the lists of tests by submitting comments on the notice. Under the rulemaking procedures of the Administrative Procedures Act, the EPA is required to take this information into account before publishing a final rule. The final rule will indicate the deadline for the submission of test reports. If the industry is still unsatisfied with the test rule, suit can be brought against the EPA. Many lawsuits have been brought against the EPA on Section 4 matters.

The tests must be done according to guidelines published under TSCA. The EPA has established dozens of test guidelines for health and environmental effects and environmental fate. As part of a deregulation effort, the EPA has removed these guidelines from 40 CFR Part 798 and now makes these available on their website with cross reference to OECD methods. The tests need to be conducted according to GLP regulations (40 CFR Part 799).

The EPA has noted the need for testing besides the recommendations of the ITC. Some US laws lack authority to require regulated industries to conduct testing that various regulatory agencies

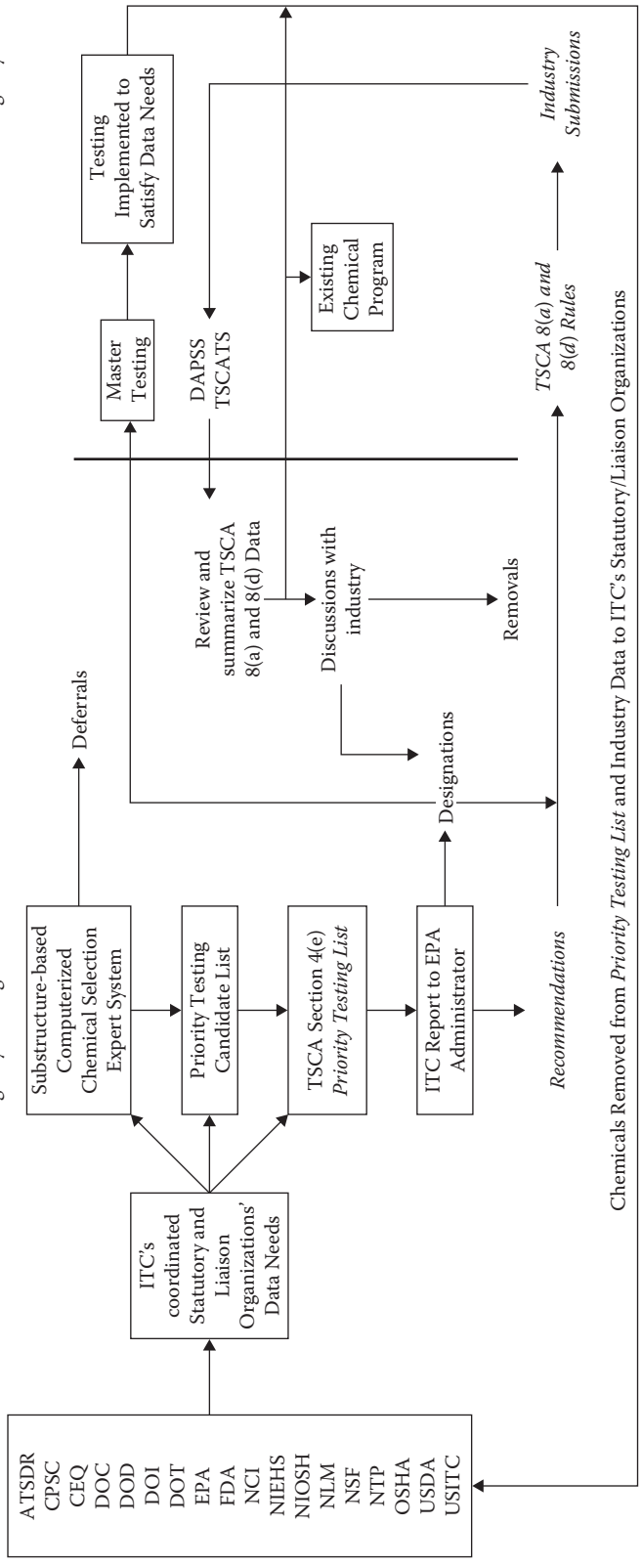

FIGURE 10.4 Schematic of process to develop Section 4 test rules.

TABLE 10.6
Categories of Chemicals and Exposure Situations Added to the EPA's Master Test List in 1996

Persistent bioaccumulators
New chemicals program "Chemical Categories"
EPCRA Section 313 ("Tri Screening")
Clean Air Act Section 112 "Air Toxics" (hazardous air pollutants)
SARA Section 104 "Priority Data Needs"
Respirable fibers
Indoor air source characterization—carpet/carpet-related products
Indoor air source characterization—interior architectural coatings
Polychlorinated dioxins/furies in wood pulp/paper mill sludge
Endocrine disrupters (new category)
Machining fluid products/chemicals (new category)
Paint stripping products use cluster (new category)
Oxygenated fuel additives (new category)

may feel are necessary to determine public health risks of various industrial activity. OPPT has proposed testing initiatives under Section 4 authority for data needed by Occupational Safety and Health Administration (OSHA) for determining the potential for skin absorption of certain chemicals (Federal Register, 1999b) and for the EPA's Office of Clean Air for further information on certain hazardous air pollutants (Federal Register, 1996). The Agency for Toxic Substances and Disease Registry (ATSDR), the National Toxicology Program (NTP), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) expect test rules to be developed for gathering necessary data on several chemicals (Federal Register, 1999c). Usually these initiatives encounter delay in the regulatory process. The EPA has more recently encouraged voluntary test programs. The EPA tracks all of these testing programs on various chemicals through a Master Testing List. More recent additions of chemical categories added to the Master Testing List illustrate the breadth of programs that is being considered. Categories added since 1996 are listed in Table 10.6.

The EPA is expended much of its resources on two major testing initiatives. One relates to recent concern about toxicity of various chemicals to humans and wildlife through mechanisms of action that may affect endocrine systems. This concern has led to the passage of the Food Quality Protection Act and amendments to the Safe Drinking Water Act that require the EPA to develop screening tests and implement a program to screen various chemicals for biological activity which target endocrine systems. Although the main focus of this program will be on pesticides, these new laws give the EPA the legal authority to address chemicals that have been found to contaminate drinking water sources. As of this writing, the screening tests are still under development. It is unclear to what extent the EPA will require screening of industrial chemicals (Federal Register, 1998a, b).

The second new program is much further along. In 1998, the EPA requested voluntary testing of High Production Volume (HPV) chemicals. The EPA defines HPV chemicals as those that are manufactured at an annual volume more than one million pounds. The EPA is focusing on a list of approximately 2,800 nonpolymeric organic chemicals that exceed this production limit. The EPA requested that companies volunteer for this program by December 1, 1999. In addition, the EPA has worked with various industry and trade associations and foreign regulatory authorities to make this testing effort more of an international effort. This effort was quite successful since EPA only needed to address approximately 40 chemicals in its proposed test rule that lacked volunteers (Federal Register, 2000).

The HPV testing program is modeled after the voluntary OECD Screening Information Data Set (SIDS) Program. The SIDS battery was developed by regulatory toxicologists as the minimum data needed to screen HPV chemicals for health and environmental concerns. Approximately 400 chemicals have been addressed in the SIDS program, however, only about 100 have completed the entire process culminating in peer review (OECD, 1981).

Whether every test in the SIDS battery needs to be conducted on each chemical on the list is a controversial subject. The SIDS program and the EPA have published guidance for using category approaches for structurally related chemicals (EPA, 1999a, b). This guidance attempts to define how scientific judgment can be used to determine whether data on similar chemicals is sufficient to estimate the hazard potency of structurally similar chemicals. Most consortiums were formed to address various classes of chemicals. Several test programs were submitted in the latter half of the year 2000. It will be interesting to see how aggressive the test proposals will be in the use of the category approach to minimize test costs. The HPV testing program will be the most expensive test program ever used through the TSCA Section 4 authority.

The EPA and industry have allied to make all the information generated in the HPV program available through the Internet. Industry participants will make robust summaries of preexisting and newly generated data in a publicly available database. Testing proposals will also be made public. It is expected that these proposals will be scrutinized not only by the EPA, but also by public interest groups, especially the Environmental Defense Fund (EDF) and People for Ethical Treatment of Animals (PETA). The point of view of these public interest groups is diametrically opposed. EDF called for an increased level of testing by industry to support the safety of their chemicals in a report entitled *Toxic Ignorance* (Environmental Defense Fund, 1997). PETA on the other hand, believes that the testing required is unnecessary and will cause unnecessary pain and suffering to laboratory animals. The proper level of testing promises to become an interesting public debate (EPA, 1999b). It is also expected that, as more data emerges on the HPV chemicals, increased awareness about the hazards of chemicals will result in further discussion about the safety of these chemicals to health and the environment.

Sections 6 and 7: Existing Chemicals Control

If new test data or information indicate that control of a chemical is needed to protect health or the environment, TSCA gives the EPA the authority to take a wide variety of actions under Sections 6 and 7.

This authority includes limiting or banning the manufacture and use of chemicals for just cause depending on the seriousness of the effect and the appropriateness of the action. When TSCA went into effect, it was originally thought that the EPA would often act to limit the use of chemicals because of data submitted under Section 4 and other reporting rules. However, little action has been taken under Sections 6 and 7. The EPA has taken final action only on PCBs, fully halogenated chlorofluorocarbons and asbestos.

The lack of EPA action is due to a variety of causes. Often, industry takes voluntary action to move onto substitute chemicals when a serious problem arises. It is also difficult to determine if the actual exposure to certain chemicals warrants regulatory action. The EPA also has found that it is difficult to take action under Sections 6 and 7 due to the formal rulemaking procedures in TSCA that require the EPA to identify the most cost-effective regulatory approach, consider the benefit of the chemical, and assess the availability of substitutes for the chemical.

In 1991, parts of the EPA ban and limits on asbestos were overturned due to a court ruling in which the EPA failed to properly assess the economic burden of the rule as well as assess alternate solutions (Corrosion Fittings vs. The EPA, 1991). Critics of industry and the EPA say that the success of this lawsuit indicates that TSCA is too weak to effectively limit chemicals. However, since the asbestos regulations were deliberated internally at the EPA for 10 years before they were

published, a little criticism of the agency on its inability to establish a successful review framework to use Section 6 authority would seem to be justified to a certain extent.

Recently, the EPA has tried to develop criteria and procedures to manage and prioritize the review of existing chemicals. A phased risk management has been developed (EPA, 1992). Chemicals are first assessed at a cursory level called RM1. The EPA asks industry to voluntarily supply exposure information to help assess the risks. After RM1 is complete, later phases pursue the investigation in greater detail (RM2 and post RM2 stages). After RM1 review, the EPA sometimes asks for voluntary controls or for exposure studies for data that will be used in the further review. The EPA is also concentrating on more limited action on the highest risk activities for a chemical; such as the use of neurotoxic and carcinogenic acrylamide monomer in sewer-grouting operations (Federal Register, 1991) and the use of nitrosamine-forming nitrites in metalworking fluids (Federal Register, 1993). The EPA has also started a number of cooperative, voluntary programs to reduce the risk of chemicals in certain industries.

Section 8: Reporting Rules

There are a wide variety of reporting rules in Section 8 of TSCA. The purpose of these rules is for the EPA to gather information from industry on the uses and hazards of chemicals. Section 8(a) rules gather information on the use and manufacture of chemicals. Section 8(b) is the authority that the EPA used to require reporting to compose the original TSCA Inventory of Chemical Substances. Section 8(c), 8(d) and 8(e) deal with the reporting on the health and environmental effects of chemicals. Because the latter three sections are of more interest to toxicologists, they will be covered in more detail here.

Section 8(c): Adverse Reaction Reporting

Various US laws require manufacturers to keep records on and report adverse reactions to products. Probably the most elaborate example is the requirement of the Food, Drug, and Cosmetic Act on drug manufacturers (see Chapter 2).

Similar requirements are delineated in Section 8(c) of TSCA. Manufacturers, importers and processors of chemicals are required to keep records of allegations of health and environmental effects. These records must be kept for at least 5 years, and in the case of employee health effects, for at least 30 years. The regulations governing this section require recording the allegation of an effect on health or the environment regardless of proof.

Industrial toxicologists responsible for Section 8(c) compliance need to make sure that internal company reporting mechanisms for incidents involving employees, plant neighbors, and customer complaints keep them informed of all allegations. These records are required to be kept in a central location at the company. When investigating a particular chemical, the EPA can require companies to submit copies of the allegations on the chemical to the agency. The EPA has rarely invoked this reporting requirement.

Section 8(d): Health and Safety Data Reporting

The legislative history of TSCA acknowledges that industry conducts many voluntary health and safety studies, but these are rarely published in the scientific literature. It is important that the EPA have access to all health and safety data when the investigation of a chemical reaches a certain point. The EPA routinely adds to the list of reportable substances in 40 CFR 716.120 after receiving an ITC report.

When a new Section 8(d) rule becomes effective, manufacturers, importers, and processors of any newly listed chemical have 60 days to report all health and safety studies in their files. In some

cases, only a list of studies is required, but if the report is readily available to the company, a copy of the full report is usually required. The EPA recently made a number of improvements to the procedural rule for reporting to make the process more efficient, including shortening the period for continued reporting of new studies from 10 years to 1 year (Federal Register, 1998c). Exceptions to this are possible for up to two years on a chemical-by-chemical basis. Sunset dates are included for every chemical listed in 40 CFR 716.120. Federal Register notices on ITC reports now routinely request that industry submit available unpublished data before the Section 8(d) rule is published to help expedite the review of newly listed chemicals.

The regulatory definition of a health and safety study is complex and occupies approximately a half page in the Code of Federal regulations (40 CFR 716.3). It includes not only laboratory toxicology and environmental effect and fate studies, but also certain industrial hygiene studies, environmental monitoring studies, and computer modeling studies. As with all TSCA regulations, reporting rules and procedures are complex and 40 CFR Part 716 should be consulted to assure proper and complete reporting.

Section 8(e): Substantial Risk Reporting

Section 8(e) of TSCA requires manufacturers, importers, and processors of chemicals to immediately submit to the EPA any information that may indicate a substantial risk to health and the environment. These reporting requirements assure that the EPA is immediately notified of studies or of incidents that may need quick remedial regulatory action. The EPA first published guidelines on the reporting requirements in 1978 (Federal Register, 1978). A summary of the guidelines is given in Table 10.7.

During the first decade of the existence of TSCA, the EPA took surprisingly little action based on substantial risk reports that were submitted. Industry submitted hundreds of reports based on the vague 1978 guidelines. Although the EPA action was largely absent, there was much interchange of information among companies that manufactured, purchased and used a particular chemical after submittal of a substantial risk report. The submitting company found that it is necessary due to the public nature of the reports to reassure customers about the safety of the chemical or updated safe handling recommendations.

After a number of inspections of corporate records, the EPA felt that not all substantial risk information had been reported. The EPA issued new, more specific guidance in 1991 (EPA, 1991b). These guidelines were issued in conjunction with a voluntary Compliance Audit Program (CAP) in which much of the regulated industry participated.

Highlights of the 1991 guidance are outlined in Tables 10.8 through 10.10. Unfortunately, the new guidelines encourage the reporting of information that many toxicologists consider trivial. Some examples of overly conservative guidance include evidence of neurotoxicity at virtually any dose or exposure route and organ toxicity observed at high doses in repeated dose studies.

The volume of reporting has increased due to the new guidelines. Under CAP, over 7,000 reports were submitted between 1991 and 1993. Although this increases the amount of information available to EPA scientists and the public, the net effect of the new guidelines as judged by this author is counterproductive, since substantial risk reports no longer have the same significance. Due to the trivial nature of most new reports, companies in industries that use chemicals have become increasingly more complacent about the substantial risk reports of their suppliers.

As of this writing, the EPA is still working on revising the guidance for companies to report environmental accidents (Federal Register, 1999d). The only recent action under Section 8(e) is defining the nature of endocrine disruption effects that require reporting (Federal Register, 1998a–c). It is uncertain whether the EPA will conduct another comprehensive review of the reporting criteria in the future.

TABLE 10.7
1978 Substantial Risk Reporting Guidance: March 16, 1978 Federal Register

V. What constitutes substantial risk
The agency considers effects for which substantial risk information must be reported to include the following:

a. *Human health effects*
   1. Any instance of cancer, birth defects, mutagenicity, death, or serious or prolonged incapacitation, including the loss of or inability to use a normal bodily function with a consequent relatively serious impairment of normal activities, if one (or a few) chemical(s) is strongly implicated
   2. Any pattern of effects or evidence which reasonably supports the conclusion that the chemical substance or mixture can produce cancer, mutation, birth defects or toxic effects resulting in death, or serious prolonged incapacitation

b. *Environmental effects*
   1. Widespread and previously unsuspected distribution in environmental media, as indicated in studies (excluding materials contained within appropriate disposal facilities)
   2. Pronounced bioaccumulation. Measurements and indicators of pronounced heretofore unknown to the Administrator (including bioaccumulation in fish beyond 5,000 times water concentration in a 30-day exposure or having an *n*-octanol/water partition coefficient greater than 25,000) should be reported when coupled with potential for widespread exposure and any nontrivial adverse effect
   3. Any nontrivial adverse effect heretofore unknown to the Administrator, associated with a chemical known to have bioaccumulated to a prolonged degree or to be widespread in environmental media
   4. Ecologically significant changes in species' interrelationships; that is, changes in population behavior, growth, survival, and so on, that in turn affect other species' behavior, growth, or survival
      Examples include
      i. Excessive stimulation of primary producers (algae, macrophytes) in aquatic ecosystems, for example, resulting in nutrient enrichment, or eutrophication, of aquatic ecosystems
      ii. Interference with critical biogeochemical cycles, such as the nitrogen cycle
   5. Facile transformation or degradation to a chemical having an unacceptable risk as defined earlier

c. *Emergency incidents of environmental contamination*—any environmental contamination by a chemical substance or mixture to which any of the aforementioned adverse effects has been described and which because of the pattern, extent, and amount of contamination:
   1. Seriously threatens humans with cancer, birth defects, mutation, death or serious or prolonged incapacitation, or
   2. Seriously threatens nonhuman organisms with large-scale or ecologically significant population destruction

VI. Nature and sources of information which *reasonably supports the conclusion* of substantial risk

1. Designed, controlled studies
   a. In vivo experiments and tests
   b. In vitro experiments and tests
   c. Epidemiological studies
   d. Environmental monitoring studies
2. Reports concerning and studies of undersigned, uncontrolled circumstances
   a. Medical and health surveys
   b. Clinical studies
   c. Reports concerning and evidence of effects in consumers, workers, or the environment

TABLE 10.8
1991 Substantial Risk Reporting Guidance: Neurotoxicity Observations in General Toxicology Studies

I. Not serious
   1. Effects only seen in moribund animals or in only one or a few isolated cases in non-moribund animals.
   2. Effects which are transient in nature, rather than intermittent or continuous

II. Probably not serious, but may be supportive evidence of neurotoxicity if observed with more serious effects
   1. Lethargy
   2. Salivation

III. Serious effects, if not judged non-serious by I
   1. Paralysis
   2. Convulsions
   3. Ataxia

TABLE 10.9
1991 Substantial Risk Reporting Guidance: Table 10.1—Factors to Consider in Determining Reportability of Lethality Information Under TSCA Section 8(e)

LD_{50} Oral Dose (mg/kg)	LD_{50} Dermal Dose (mg/kg)	4-h LC_{50} Inhalation Dose (ppm/mg/l)	Consider Exposure/Other Factors?
5	20	<50 (0.5)	No (EXTREMELY TOXIC)
>5–50	>20–200	>50 (>0.5) to 200 (2)	Only to some reasonable degree (HIGHLY TOXIC)
>50	>200	>200 (>2)	Yes (MODERATELY TOXIC)

Public Databases Maintained by the Environmental Protection Agency for Toxic Substances Control Act Data

The EPA compiles data submitted under Sections 4 and 8 reporting rules in a database called Toxic Substances Control Act Test Submissions (TSCATS). This database is extremely useful to toxicologists in locating data not published in the scientific literature. The database can be accessed directly through the Internet via the EPA's website.

European Union

In 1993, The European Council instituted a comprehensive review of existing chemicals under the Dangerous Substances Directive (European Commission, 1993b). This directive calls for a risk assessment approach on priority chemicals. Reporting of use and health information by European chemical companies was required in three phases. Tiers of production volume established the phases with highest volume chemicals reported first. The regulation obliges industry to submit all readily available data on HPV.

TABLE 10.10
1991 Substantial Risk Reporting Guidance

Summaries called status reports were issued on each 8(e) report received before 1991. As part of the 1991 guidance, the EPA cataloged the most important status reports by category. These categories are illustrative of the breadth of information subject to 8(e) reporting.

SECTION 8(e) GUIDANCE/POLICY REFLECTED IN STATUS REPORTS

1. Toxicological/exposure findings
   a. Acute toxicity (animal)
   b. Acute toxicity (human)
   c. Subacute toxicity (animal)
   d. Immunotoxicity (animal)
   e. Neurotoxicity (animal)
   f. Neurotoxicity (human)
   g. Oncogenicity (animal)
   h. Oncogenicity (human)
   i. Reproductive/developmental (animal)
   j. Reproductive/developmental (human)
   k. Genotoxicity *(in vitro)*
   l. Genotoxicity *(in vivo)*
   m. Aquatic toxicity/bioconcentration
   n. Emergency incidents of environmental contamination
   o. General/nonemergency environmental contamination
2. General reporting issues
   a. Intracorporate reporting procedures
   b. Subject persons
   c. Subject chemicals
   d. Research and development chemicals
   e. Drug export
   f. Pesticide export
   g. Previous manufacture/import/process/distribution
   h. Obtaining information
   i. Pre-1977 information
   j. Actual knowledge by the EPA
   k. Published scientific literature
   l. Information obtained from other federal agencies
   m. Information corroborating well-established effects
   n. Relationship to other TSCA reporting requirements
   o. Relationship to other the EPA administered authorities
   p. Relationship to authorities not administered by the EPA
   q. Section 8(e) reporting procedures

The International Uniform Chemicals Information Database (IUCLID) database is a repository of the reported information and a tool for setting priorities for further risk assessment. European chemical companies and regulatory authorities are expected to cooperatively participate in the worldwide HPV chemicals testing effort through the International Council of Chemical Associations (ICCA). Article 10 of the directive mandates that the real or potential risk for man and environment of priority substances is to be assessed using principles laid down in Commission Regulation (EC) No. 1488/94 (European Union, 1994) on risk assessment for existing substances. The risk assessments are carried out by competent authorities designated by the responsible member states to act as rapporteurs. An extensive technical guidance document was published on the risk assessment

process in 1996 (European Commission, 1996). A schematic of the risk assessment process and range of outcomes on particular chemicals is given in Figure 10.2.

Four priority lists of substances have been listed since 1995 under existing substances regulation 793/93/EEC. Each list consists of 30–50 substances. A rapporteur from a member country is appointed. Action has been slow on the priority lists so far. Many of the chemicals on the first and second lists have not proceeded beyond the preliminary discussion stage. In addition, the European Commission has published a document outlining an action plan for endocrine disrupters (European Commission, 1999) as well as studying regulatory actions for Persistent Organic Pollutants (POPs).

Although no formal authority exists in the DSD to mandate testing on existing substances, it would be possible to seek voluntary testing on any of the chemicals on the priority lists. The DSD differs from TSCA in that it does not contain reporting requirements for new risk information or the recording of adverse reaction reports.

Although EU laws and directives were meant to supersede national laws, this has happened very slowly. The Scandinavian countries and Germany have been more persistent in retaining their national initiatives on industrial chemicals than other member states. Many times, this activity will catalyze additional new regulations in the EU similar to the way various states, such as California, spur reform in the US.

Japan

The Japanese law also gives the implementing agencies authority over existing chemicals. The same criteria and procedures used to classify chemicals as designated substances are used (see Figure 10.3). There are currently nine Class I and 23 Class II Specified Substances listed which consist mainly of PCBs and other chlorinated hydrocarbons and pesticides as well as a number of organotin compounds. Class I compounds are banned practically speaking and Class II compounds can only be marketed under tight controls. Currently, those new chemicals that become Designated Substances as a result of a review of data presented by an intended manufacturer are merely being tracked. However, they can be subject to restrictions if concern about any of these chemicals increase. As this chapter went to press, approximately 10 designated substances were being reviewed for more stringent controls.

The Japan Environment Agency is actively studying the endocrine disrupter issue. A list of 67 suspected endocrine disrupters has been published and an environmental monitoring program is in place. It is likely that any risk management actions to protect public health and the environment will be coordinated with international efforts (Japan Environment Agency, 1998).

Canada

Because the CEPA is a relatively new law, regulatory programs on existing chemicals have not progressed to a great extent in Canada. Much control is exerted through hazard communication authority (see Chapter 11). Substantial risk reporting similar to TSCA is required under Section 17 of CEPA. Guidelines have been published for submission of these reports (Environment Canada, 1994).

Australia

During 1997 and 1998, several legislative and streamlining activities were introduced into the Existing Chemicals Assessment Program. These introduced greater flexibility in the declaration of Priority Existing Chemicals (PECs) and facilitated preliminary assessments. Assessments of only six existing chemicals were published in prior years. Candidate chemicals can be nominated by

industry, the public, or government. After a review of 41 candidate chemicals, eleven were declared as priority substances in 1978. This process of declaring PECs carefully focuses on chemicals that are extensively used in Australia and avoids chemicals that are subject to review in other countries to conserve resources. Additional information and input from industry is solicited during the process. A preliminary or full quantitative risk assessment is done as part of the review of PECs (NOHSC, 1999).

Recently, there has been more evidence of activity on a wider variety of generic existing chemical topics, such as endocrine disruption and the HPV issue on the NOHSC website.

New Zealand

Risk Assessment Frameworks are published and available under the Department of Food Safety and the New Zealand Environmental Protection Authority. The reader is encouraged to visit the site for more information. The New Zealand Environmental Protection Agency has its own historical classification system, including the Chemical Classification and Information Database (CCID) that maintain classifications according to Hazardous Substances and New Organisms (HSNO) regulations. Chemicals allowed in New Zealand are managed on the New Zealand Inventory of Chemicals (NZIoC).

Philippines

The Philippines has a Priority Chemical List (PCL). It currently lists 28 chemicals. As DENR reviews new chemicals, some may be added to this PCL if determined to pose unreasonable risk to public health, workplace and the environment. These chemicals are subject to Chemical Control Orders (CCOs) that can prohibit, limit or regulate the use, manufacture, import, export, transport, processing, storage, possession and wholesale of the chemicals.

Outlook for the Future

It is likely that REACH-like regulations will continue and become more globalized in approaches. At least three major issues will be the focus into the twenty-first century.

1. *Endocrine toxicity*: Although the US regulatory agencies are focusing on validating screening tests before moving on with a regulatory program, the European Commission may begin regulating certain suspect chemicals before definitive data is obtained. Whether the dangers of the current level of endocrine modulators in the environment are judged to be sufficiently serious to justify regulatory action as new data is generated will be an interesting debate. The current US Endocrine Disruptor Screening Program will likely continue for many decades.
2. The use of In Vitro and Computational Toxicology Testing Methods for regulatory decision making, given the high cost, long timetables, and limited resources involved in animal testing, as well as the long term regulatory discussions.
3. PBT/POP chemicals. Regulatory programs will continue to emerge in the US and Europe that will begin to focus on existing chemicals that may be problematic because of their environmental persistence.

These and other issues will be on the forefront of activity. As always, political agendas and socioeconomic events will also play an important role in defining the future of chemical control regulations.

Websites of Interest

Governments	
Australia (NOHSC)	www.nohsc.gov.au
Canada (Environment Canada)	www.ec.gc.ca
Japan (MITI)	www.miti.gd.jp
Korea	www.infokorea.com
Philippines (DENR)	www.denr.gov.ph
EPA	www.epa.gov
US Government Printing Office	www.gpo.gov
Other organizations	
Chemical Abstracts Services (CASs)	www.cas.org
Chemical Manufacturers Associations (CMA) (now the American Chemistry Council)	www.cmahq.com
Environmental Defense Fund (EDF)	www.edf.org
Office for Economic Cooperation and Development (OECD)	www.oecd.org
International Council of Chemical Associations (ICCA)	www.icca-chem.org
United Nations Environmental Programs (UNEP)	www.unep.org

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11 Industrial Chemicals

Hazard Communication, Exposure Limits, Labeling and Other Workplace and Transportation Requirements under Occupational Safety and Health Administration, Department of Transportation, and Similar Authorities around the World

Edward V. Sargent

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INTRODUCTION

Occupational toxicology is a subdiscipline of toxicology concerned with the health effects of chemicals encountered in the workplace. While the focus of this chapter is primarily industrial chemicals, the ultimate goal of the occupational toxicologist is to define the hazards of handling all types of industrial chemical raw materials, process intermediates, and finished products in order to determine appropriate handling practices. To achieve this goal, the toxicologist must work closely with professionals in industrial hygiene, occupational medicine, and engineering to integrate health and safety risk with regulatory concerns of manufacturing, packaging, classification, labeling, and transportation of goods.

Occupational toxicology testing programs have been established to provide sufficient information to those responsible for assuring the safe handling of new products and associated intermediates. There appears to be little difference between industrial chemical, petrochemical, and pharmaceutical industries in terms of the general approach and implementation of these programs despite differences in

regulatory requirements. Good occupational toxicology programs are often less driven by regulation and more by internal requirements for new chemical product development. Occupational toxicology programs are considered an integral part of good chemical product stewardship (Sargent et al., 2015).

HAZARD COMMUNICATION

Hazard communication is a cornerstone of many of the recent occupational safety and health laws, both in the United States and overseas. The largest portion of the occupational toxicologist's time may be spent evaluating and communicating hazard information to employees who have a need (and a right) to know about the hazards of the chemicals handled in their workplace. Hazard communication and right-to-know laws provide the barest minimum of how, what, and to whom we should communicate. Not only do workers directly handling chemicals need to know and understand risks, their supervisors and management need to know as well.

In order to protect the health of employees who may be exposed to chemical substances as well as to maintain the registration of chemicals in countries where they are placed in commerce, the toxicologist is required to develop a hazard assessment program, which: (1) provides recommendations for employee protection; (2) provides data for preparation of safety data sheets (SDS) and labels; (3) classifies the material for transportation purposes; (4) derives occupational exposure limits (OELs); (5) completes chemical testing required by regulation; (6) develops emergency response plans; and (7) guides industrial hygiene, safety, and medical surveillance programs. Toxicology testing of products is generally required by regulation or guided by product stewardship or the potential for product liability.

Hazardous materials are defined and regulated in the United States primarily by laws and regulations administered by the US Environmental Protection Agency (EPA), the US Occupational Safety and Health Administration (OSHA), the US Department of Transportation (DOT), and the US Nuclear Regulatory Commission (NRC). Each with its own definition of a hazardous material. OSHA's definition covers any substance or chemical, which is a *health hazard* or *physical hazard*, including: chemicals that are carcinogens, toxic agents, irritants, corrosives, sensitizers; agents which act on the hematopoietic system; agents which damage the lungs, skin, eyes, or mucous membranes; chemicals which are combustible, explosive, flammable, oxidizers, pyrophoric, unstable-reactive, or water-reactive; and chemicals which in the course of normal handling, use, or storage may produce or release dusts, gases, fumes, vapors, mists or smoke which may have any of the previously mentioned characteristics. EPA incorporates the OSHA definition and adds any item or chemical that can cause harm to people, plants, or animals when released by spilling, leaking, pumping, pouring, emitting, emptying, discharging, injecting, escaping, leaching, dumping, or disposing into the environment. The 40 Code of Federal Regulations (CFR) 355 contains a list of over 350 hazardous and extremely hazardous substances. DOT defines a hazardous material as any item or chemical that, when being transported or moved in commerce, is a risk to public safety or the environment and is regulated as such under its Pipeline and Hazardous Materials Safety Administration regulations (49 CFR 100-199), which includes the Hazardous Materials Regulations (49 CFR 171-180). In addition, hazardous materials in transport are regulated by the International Maritime Dangerous Goods Code; Dangerous Goods Regulations of the International Air Transport Association; Technical Instructions of the International Civil Aviation Organization; and US Air Force Joint Manual, Preparing Hazardous Materials for Military Air Shipments (IHHM, 2015).

Depending on the type of substance or product, that is, pharmaceutical, pesticide, bulk synthetic chemical, or petrochemical, chemical testing requirements can also be mandated or guided by any number of regulations including the US Federal Food, Drug, and Cosmetic Act; Federal

Insecticide, Fungicide, and Rodenticide Act (FIFRA); and the Toxic Substances Control Act (TSCA); or the European Regulation concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (EC Regulation, 2006, UK Health and Safety Executive, 1991, US Environmental Protection Agency, 1982a, 1982b, 2008). In contrast to European REACH legislation and other national regulations (e.g., China) concerning the registration, evaluation, and authorization of chemicals outlining, in many cases, specific testing requirements, the US has no such requirements specified by governmental agencies regulating hazardous chemicals in the workplace. The EPA has worker safety standards for those who use pesticides and several worker-related studies that need to be conducted for pesticide registration, while general chemicals may have no such data requirements.

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

The US has been one of the world leaders for legislation and regulation on matters of workplace safety. The Occupational Safety and Health (OSH) Act of 1970 arose as a result of two decades of increasing concern about hazards in the workplace. The OSH Act established the Occupational Safety and Health Administration (OSHA) in the Department of Labor (DOL) and the National Institute for Occupational Safety and Health (NIOSH) in the former Department of Health, Education, and Welfare (DHEW). The OSH Act restructured numerous existing programs in order to establish uniform health and safety standards applicable to all businesses affecting interstate commerce. Within the US Department of labor, OSHA is responsible for promulgating and enforcing occupational and safety standards and regulations.

The OSHA Hazard Communication Standard (HCS) (United States Department of Labor, 1985) is representative of one type of performance-oriented standard among occupational safety and health regulations. The standard requires chemical manufacturers to evaluate the hazards of chemicals they produce or import. Based on the hazard evaluation, the Standard requires that labels and SDSs be prepared according to specified criteria to convey hazard information and protective measures to employees and downstream users. The HCS is considered a performance-oriented regulation because it covers all hazardous chemicals and types of employment, but, other than specifying classification of hazards, selection of hazard phrases, and labeling content, does not stipulate how to comply with its requirements. HCS does not require testing of materials, but rather relies on available data. Under the ‘General Duty’ clause of the OSH Act of 1970, the manufacturers are clearly responsible for maintaining a safe workplace and consequently using all available data for evaluating the hazards of materials produced.

Similar legislative, administrative, and regulatory measures to ensure safe handling of chemicals have been adopted in many countries. Unfortunately, this resulted in diverse multiplicity of hazard classifications creating confusion at the end-user level due to the differences found in SDSs and labels for the same chemical (Winder et al., 2005). Differences in classification also resulted in confusion in packaging and labeling for transport. At the 1992 Rio Earth summit offered recommendations for a globally harmonized system (GHS) for classification and labeling of hazardous chemicals. The GHS system included consistent classification and labeling of chemicals, SDSs, and more easily understandable symbols for labeling as well as manufacturing, transport, and disposal of chemicals.

In March 2012, OSHA revised its Hazard Communication Standard to align it with the United Nations GHS of Classification and Labeling of Chemicals, Revision 3. This revision to HCS built on the existing standard by requiring chemical manufacturers and importers to follow specific criteria when evaluating the hazardous chemicals and when communicating the hazards through labels and SDSs.

HAZARD COMMUNICATION OUTSIDE THE UNITED STATES

In 1986, Canada implemented the Workplace Hazardous Material Information System (WHMIS 1988). Like the OSHA HCS, WHMIS requirements include: criteria to identify hazardous materials and to provide information about them in the workplace; labeling and SDS, training requirements; and a system to protect proprietary information. WHMIS is much less performance-oriented than OSHA HCS. Again, no specific testing is required, but the product or material must be properly evaluated to determine if it is a *controlled product*. WHMIS has specific format requirements that have forced companies to change their labels so they can ship chemicals to Canada. While Canada participated in the negotiations and ultimate drafting of the GHS, it has yet to incorporate the enabling legislation into WHIMS.

The European Union (EU) and its member states have had workplace labeling requirements since 1967 (EC Council Directive 1967). A community-wide SDS and specified mandatory 16-section format have also long been in place. Like WHMIS and HCS, the labeling requirements and the SDS format are specified. On June 1, 2007, these two pieces of legislation were superseded by an integrated European Community Regulation on chemicals and their safe use—*REACH*—which establishes the European Chemicals Agency (ECHA) and deals with the registration, evaluation, authorization, and restriction of chemical substances. REACH also incorporates elements of chemical inventory management, mandatory testing requirements, and hazard communication. The specific hazard classification criteria within the EU are codified in the Regulation on Classification, Packaging and Labeling (CPL; EC Regulation No. 1272/2008).

Safe Work Australia was established by the Safe Work Australia Act 2008 with primary responsibility to lead the development of policy to improve work health and safety and workers' compensation arrangements across Australia. Safe Work Australia began operating as an independent Australian Government statutory agency on November 1, 2009. As a national policy body, Safe Work Australia does not regulate work health and safety laws. The Commonwealth, states and territories retain responsibility for regulating and enforcing work health and safety laws in their jurisdiction. Since the introduction of the National Occupational Health and Safety Commission (NOHSC) National Model Regulations for the Control of Workplace Hazardous Substances (1994) and the Dangerous Goods Standard (2017), hazardous chemicals have been classified by the Approved Criteria for Classifying Hazardous Substances and the Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code) (Australian Government, 1994). In 2012, following the adoption of the model Work Health and Safety Regulations, Australia began to transition to the GHS of Classification and Labelling of Chemicals, an international system used to classify and communicate chemical hazards. Australia has adopted the 3rd revised edition of the GHS under the model work health and safety laws. The GHS will become fully functional in 2017 (Australian Government, 2014).

CHEMICAL REGISTRATION

In the United States, toxicity or environmental testing can be required by the EPA under several sections of the TSCA (US Environmental Protection Agency 1994). For example, under Section 4(a) of TSCA, the EPA must require testing of a chemical substance to develop health or environmental data if the EPA finds that certain criteria are met. Manufacturers are also required under Section 8(e) to report significant adverse health effects or toxicity results. TSCA also requires that reports of toxicology studies be submitted when they are available. However, testing to identify potential occupational health hazards is not required by TSCA.

The EPA has authority over chemical substances through several acts. TSCA gives EPA authority over industrial chemicals through all stages of their lifecycle: research and development, manufacturing, distribution, and in some cases, disposal. The key sections of TSCA include the following:

Section 4: Allows EPA to require companies to perform testing on specific compounds that EPA believes could pose a risk to human health or the environment.

Section 5: Requires premanufacture notifications for new chemicals not on the EPA's master inventory; significant new use rules (SNURs) for specific uses of existing chemicals; and the use of consent orders to restrict or control manufacturing of a new compound.
Section 6: Allows EPA to restrict or prohibit manufacturing and use of chemicals (e.g., PCBs).
Section 8(a): Requires submission of data on certain chemicals that have been identified as needing further testing due to actual or potential toxicity.
Section 8(b): Requires submission of data to update the TSCA inventory.
Section 8(c): Covers allegations of significant adverse reactions and requires that a facility record be maintained registering any allegations of unknown adverse reactions that are limited to a chemical substance.
Section 8(d): Covers health and safety reporting and focuses on obtaining unpublished data from the regulated community.
Section 8(e): Requires reporting of information on chemical substances, which may pose a risk to human health and the environment.

Chemical notification requirements are generally intended for more than occupational health purposes. Furthermore, TSCA and other requirements for notification of new substances are not applicable to all types of chemical substances. For TSCA, pharmaceutical products (intermediates and raw materials) are exempt in Section 3 because they are regulated by the US Food and Drug Administration (FDA). In contrast, the TSCA exemption for pesticides regulated under FIFRA extends only to the final product.

Chemical notification requirements for the EU are stipulated in the *REACH* regulation, which deals with the registration, evaluation, authorization and restriction of chemical substances. Unlike earlier legislation, REACH places greater responsibility on the chemical manufacturer to identify and manage the risks from the chemicals they produce and to provide safety information on the substances to their employees and downstream users of these chemicals. Manufacturers and importers are required to gather information on the properties and uses of their chemical substances, perform a risk assessment, specify recommended risk management measures, and register the information in a central database run by the ECHA. The scope of the regulation significantly expands the breadth of coverage of the EU regulations by covering not only marketed substances, but also on-site intermediates, local and transported isolated intermediates, including pesticide and pharmaceutical intermediates and consumer products. REACH, which (at the time of this writing) is being phased in over an 11-year period (2007–2018), covers both new and existing chemicals essentially equivalently, requiring the manufacturer or importer to submit a technical dossier containing information on: identity, proposed uses, estimated production, acute and subchronic toxicity, environmental toxicity, physico-chemical properties, proposed hazard classification and labeling, and proposed risk management measures.

The breadth and depth of testing required is dependent on the quantity of the substance to be placed on the market. Substances manufactured at less than 1 ton per year are exempt from the regulation, and those manufactured at 1 to 10 tons require only an abbreviated base set of mammalian and genotoxicity testing, environmental fate and effects assessment, and characterization of physical properties and process safety hazards, as compared to the past. Significant emphasis has been placed on structure-activity assessment, computational modeling, and *in vitro*/*ex vivo* alternative testing. As quantities increase, additional longer and more complex tests, including reproductive, developmental, and lifetime bioassay studies may be required. A toxicokinetic analysis and more complex risk assessment must also be done. Testing requirements are reduced for site-limited and transported isolated intermediates. For chemicals possessing certain hazards—for example, carcinogens, mutagens, those causing reproductive hazards, and persistent and bio-accumulative compounds—specific chemical safety assessments must be performed, and the resultant chemical safety report is incorporated into an extended SDS. Completion of these dossier requirements and the testing they may entail is a time-consuming process, and appropriate lead time and resources must be incorporated into the research and development planning process.

TOXICOLOGY TESTING FOR PURPOSES OF TRANSPORTATION

The Hazardous Materials Transportation Act of 1974 gave the US Department of Transportation (DOT) authority to regulate the interstate transport of hazardous materials. Among other things, DOT regulates the classification of materials as to toxicity, flammability, corrosive effect, explosivity, and oxidizing potential. The DOT has adopted the classification system (HM-181) used by the International Civil Aviation Organization (ICAO) and the International Air Transport Association (IATA) to ensure that dangerous goods transported by air are labeled and packaged properly. In contrast to hazard communications standards, the DOT, as well as ICAO and IATA, regulates the safe and secure transportation of hazardous material (HazMat) in commerce. The Hazardous Materials Transportation Act and other regulations exist to protect transporters (truck drivers, rail workers, air crews, and mariners), passengers, emergency responders, and the general public from the consequences of an incident or accident involving the sudden uncontrolled release of hazmat during the cycle of transportation.

Under the DOT Hazardous Materials regulations (HMR), a product is regulated only if it is hazardous. A material is considered hazardous if it meets any one of the definitions of hazard classifications set forth by DOT. A complete description of all nine DOT hazard classes is set forth in 49 CFR Part 173, Subparts C and D. If a product or chemical meets the definition of one or more of the DOT hazard classes, then it is regulated as a DOT hazardous material (Table 11.1).

Most DOT hazard classifications are divided into Packing Groups that indicate the severity of the hazard. (Note: Combustible liquids are not assigned packing groups.) In general, there are three Packing Groups: Packing Group I—Great Danger; Packing Group II—Medium Danger, and Packing Group III: Minor Danger (USDOT, 2016). The Packing Group assignment determines the degree of care and protection required in the packaging, handling, and transportation of the material. For example: Packing Group I would be for corrosive materials that cause full thickness destruction of intact skin tissue within an observation period of up to 60 minutes starting after the exposure time of three minutes or less; Packing Group II would be for corrosive materials that cause full thickness destruction of intact skin tissue within an observation period of up to 14 days starting after the exposure time of more than three minutes but not more than 60 minutes; and Packing Group II would be corrosive materials that cause full thickness destruction of intact skin tissue within an observation period of up to 14 days starting after the exposure time of more than 60 minutes but not more than 4 hours; or that do not cause full thickness destruction of intact skin tissue but exhibit a corrosion rate on steel or aluminum surfaces exceeding 6.25 mm (0.25 inch) a year at a test temperature of 55°C (130°F).

DOT regulations for corrosivity testing call for investigation of intact skin sites only, though other protocols (Draize, FHSA, and FIFRA) called for intact, as well as, abraded sites on the skin to be evaluated. As with testing for ocular irritants, there is a growing demand, for certain in vitro and alternative tests. Some regulations, such as REACH, call for the use of in vitro dermal irritation tests (Sargent et al., 2015). Corrositex®, an in vitro method used to determine the dermal corrosive potential of chemicals and chemical mixtures, has been accepted by DOT, IATA, and Transport Canada as an alternative to animal testing for corrosivity. Corrositex is based on the ability of a corrosive chemical or chemical mixture to pass through, by diffusion and/or destruction/erosion, a biobarrier and to elicit a color change in the underlying liquid Chemical Detection System (CDS). The biobarrier is composed of a hydrated collagen matrix in a supporting filter membrane, while the CDS is composed of water and pH indicator dyes. Test chemicals and chemical mixtures, including solids and liquids, are applied directly to the biobarrier. The time it takes for a test chemical or chemical mixture to penetrate the biobarrier and produce a color change in the CDS is compared to a classification chart to determine corrosivity/noncorrosivity and to identify the appropriate DOT packing group. The DOT currently accepts the use of Corrositex to assign subcategories of corrosivity (packing groups) for labeling purposes according to United Nations (UN) Committee of Experts on the Transport of Dangerous Goods guidelines. However, the DOT limits the use of Corrositex

TABLE 11.1
Transportation Hazard Classes and Definitions

Class	Hazard	Definition
Class 1	Explosives	Explosives are any substance or article, including a device, which is designed to function by explosion or which, by chemical reaction within itself is able to function in a similar manner even if not designed to function by explosion (unless the article is otherwise classed under a provision of 49 CFR).
Class 2	Gases	Includes divisions into flammable gases; non-flammable, nonpoisonous compressed gas—including compressed gas, liquefied gas, pressurized cryogenic gas, compressed gas in solution, asphyxiant gas and oxidizing gas; and gases poisonous by inhalation.
Class 3	Flammable Liquid and Combustible Liquid	Flammable liquid means a liquid having a flash point of not more than 60°C (140°F), or any material in a liquid phase with a flash point at or above 37.8°C (100°F) that is intentionally heated and offered for transportation or transported at or above its flash point in a bulk packaging, with some exceptions. A combustible liquid means any liquid that does not meet the definition of any other hazard class, except Class 9, and has a flash point above 60°C (140°F) and below 93°C (200°F).
Class 4	Flammable Solid, Spontaneously Combustible, and Dangerous when Wet	Flammable solids include: desensitized explosives when dry are Explosives of Class 1 other than those of compatibility group A, which are wetted with sufficient water, alcohol, or plasticizer to suppress explosive properties. Self-reactive materials are materials that are thermally unstable and that can undergo a strongly exothermic decomposition even without participation of oxygen (air). Dangerous when wet material (Division 4.3) means a material that, by contact with water, is liable to become spontaneously flammable or to give off flammable or toxic gas at a rate greater than 1 L per kilogram of the material, per hour.
Class 5	Oxidizer and Organic Peroxide	
Class 6	Poison (Toxic) and Poison Inhalation Hazard	Materials, other than a gas, which are known to be so toxic to humans as to afford a hazard to health during transportation, or which, in the absence of adequate data on human toxicity: 1. Is presumed to be toxic to humans because it falls within any one of the following categories when tested on laboratory animals (whenever possible, animal test data that has been reported in the chemical literature should be used): a. *Oral toxicity*: A liquid or solid with an LD_{50} for acute oral toxicity of not more than 300 mg/kg. b. *Dermal toxicity*: A material with an LD_{50} for acute dermal toxicity of not more than 1000 mg/kg. c. Inhalation Toxicity. i. A dust or mist with an LC_{50} for acute toxicity on inhalation of not more than 4 mg/L; or ii. A material with a saturated vapor concentration in air at 20°C (68°F) greater than or equal to one-fifth of the LC_{50} for acute toxicity on inhalation of vapors and with an LC_{50} for acute toxicity on inhalation of vapors of not more than 5000 mL/m^3; or 2. Is an irritating material, with properties similar to tear gas, which causes extreme irritation, especially in confined spaces.
Class 7	Radioactive	Radioactive substances are materials that emit radiation.
Class 8	Corrosive	A corrosive material means a liquid or solid that causes full thickness destruction of human skin at the site of contact within 4 hours, or a liquid that has a severe corrosion rate on steel or aluminum.

(*Continued*)

TABLE 11.1 (*Continued*)
Transportation Hazard Classes and Definitions

Class	Hazard	Definition
Class 9	Miscellaneous	Materials which presents a hazard during transportation but which do not meet definitions of any other hazard class including: a. Any material which has an anesthetic, noxious or other similar property which could cause extreme annoyance or discomfort to a flight crew member so as to prevent the correct performance of assigned duties; or b. Any material that meets the definition for an elevated temperature material, a hazardous substance, a hazardous waste, or a marine pollutant.

TABLE 11.2
Transportation Class 6.1 Packing Group Criteria

Packaging Group	Oral Toxicity LD_{50} (mg/kg)	Dermal Toxicity LD_{50} (mg/kg)	Inhalation Toxicity by Dusts and Mists LC_{50} (1 h) (mg/l)	Inhalation Toxicity by Vapors
I	<5	≤40	≤0.5	V≥10 LC_{50} and LC_{50}≤1000 ml/m^3
II	>5–≤50	>40–≤200	>0.5–≤2	V≥LC_{50} and LC_{50}≤3000 ml/m^3, and criteria for packing Group 1 is not met
III solids	>5–≤200	>200–≤1000	>2–≤10	
III liquids	>5–≤500	>200–≤1000	>2–≤10	V≥1/5 LC_{50} and LC_{50}≤5000 ml/m^3, and criteria for packing Groups I or II are not met

to specific chemical classes, including acids, acid derivatives, acyl halides, alkylamines and polyalkylamines, bases, chlorosilanes, metal halides, and oxyhalides (National Toxicology Program [NTP], 1999).

For the purpose of transport, poisonous material (Class 6) means a material, other than a gas, which is known to be so toxic to humans as to afford a hazard to health during transportation, or which, in the absence of adequate data on human toxicity (National Toxicology Program [NTP], 2017). Definitions for packing groups for Class 6.1 toxic substances are shown in Table 11.2.

For transport, the GHS is also being applied to current transport requirements. GHS physical, acute, and environmental hazard criteria are expected to be adopted in the transport sector. Containers of dangerous goods will have pictograms that address acute toxicity, physical hazards, and environmental hazards. GHS hazard communication elements such as signal words, hazard statements, and SDS are not expected to be adopted in the transport sector (United Nations, 2005).

OCCUPATIONAL EXPOSURE LIMITS

One of the most important activities of occupational toxicology has been the establishment of occupational exposure limits (OELs) for airborne contaminants (Paustenbach 1993). The most widely used occupational exposure limits are the Threshold Limit Values (TLVs™) established by the American Conference of Governmental Industrial Hygienists (ACGIH®) (American Conference of Governmental Industrial Hygienists 2016). TLVs have largely been based on data from industrial experience, but human epidemiology studies and animal experimentation have also played an important role (Stokinger 1970). Unfortunately, the majority of chemicals used in industry do

not have exposure limits leading many companies to establish internal OELs (Galer et al., 1992, Paustenbach and Langner, 1986, and Sargent and Kirk, 1988).

The 1970 OSH Act authorized the US Secretary of Labor to:

> promulgat(e) standards dealing with toxic materials or harmful physical agents … shall set the standard, which most adequately assures to the extent feasible, on the basis of the best available science, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life.

The initial health and safety standards promulgated by US Department of Labor's OSHA in 1970 were derived from existing consensus standards established by ACGIH and the American National Standards Institute (ANSI). Many, but not all of the existing ACGIH TLVs federal standards known as Permissible Exposure Limits (PELs). Along with ANSI maximal acceptable concentrations, PELs were incorporated as federal standards in 29 CFR 1910.1000 (Table Z-2). OSHA's mandatory PELs in the Z-Tables remain in effect to date.

Since 1970, OSHA promulgated complete 6(b) standards including new PELs for 16 agents, and standards without PELs for 13 carcinogens (OSHA, 2017). Industrial experience, new developments in technology, and scientific data clearly indicate that in many instances these adopted limits are not sufficiently protective of worker health. This has been demonstrated by the reduction in allowable exposure limits recommended by many technical, professional, industrial, and government organizations, both inside and outside the United States. Many large industrial organizations have felt obligated to supplement the existing OSHA PELs with their own internal corporate guidelines. OSHA's Hazard Communication standard (1910. 1200 Appendix D) requires that safety data sheets list not only the relevant OSHA PEL but also the ACGIH TLV™ and any other exposure limit used or recommended by the chemical manufacturer, importer, or employer preparing the SDS (OSHA, 2017).

To provide employers, workers, and other interested parties with a list of alternate occupational exposure limits that may serve to better protect workers, OSHA has annotated the existing Z-Tables with other selected occupational exposure limits. OSHA has chosen to present a side-by-side table with the Cal/OSHA PELs, the NIOSH Recommended Exposure Limits (RELs) and the ACGIH TLVs. OSHA's mandatory PELs in the Z-Tables remain in effect. However, OSHA recommends that employers consider using the alternative occupational exposure limits because the Agency believes that exposures above some of these alternative occupational exposure limits may be hazardous to workers, even when the exposure levels are in compliance with the relevant PELs (Hogan and Nalbone, 2016). Cal/OSHA has established an extensive list of PELs that are enforced in workplaces under its jurisdiction. Cal/OSHA PELs are promulgated under statutory requirements for risk and feasibility that are no less protective than the OSH Act. Though not enforceable in establishments outside of Cal/OSHA's jurisdiction, the PELs can provide information on acceptable levels of chemicals in the workplace. Of all the states that have OSHA-approved State Plans, California has the most extensive list of OELs (OSHA, 2017).

ACGIH annually publishes the TLVs for its Chemical Substances Committee, which has been in existence since 1941. This activity of the ACGIH is recognized throughout the world, and the exposure recommendations of ACGIH form the underpinnings of workplace exposure regulations in many countries (Kraska, 2001). ACGIH has published over 750 TLVs since its inception. An annual notice of intended changes announces changes being considered for the following year (ACGIH, 2016). A TLV is defined as the airborne concentration of substances and conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. TLVs are established by ACGIH based on available information from industrial experiences and experimental human and animal studies. TLVs are expressed as Time Weighted Average (TWA) concentration for a conventional 8-hour workday and 40-hour workweek. ACGIH also uses the concept of Short Term Exposure Limit (STEL), which is the TWA concentration a worker can be exposed without adverse effects for 15 minutes and a ceiling (TLV-C) level is defined as the airborne concentration that should not be exceeded during any part of the work exposure. ACGIH also has

developed and incorporated notations and endnotes to further highlight potential hazards including when a biological exposure index (BEI®) is also recommended for the substance; Inhalable Fraction and Vapor (IFV) when a material exerts sufficient vapor pressure such that it may be present in both particle and vapor phases; DSEN and/or RSEN for potential to cause dermal or respiratory sensitization; and SKIN for potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and eyes (ACGIH, 2016).

The general methodology for establishing TLVs is discussed in ACGIH's annual publication and rationale for decisions on individual chemicals is documented in a compendium (ACGIH, 2016). The annual publication also lists BEIs for certain chemicals. BEIs are reference values for certain measurements in biological specimens from workers, such as urine and exhaled air, to determine their level of exposure to these chemicals. BEIs can be based on the relationship between the intensity of exposure and biological levels of the determinant or biological levels and health effects. The data used to set BEIs come from controlled or field studies with humans. Due to pharmacokinetic differences between species, animal studies are not useful to set BEIs.

The National Institute for Occupational Safety and Health (NIOSH) establishes Recommended Exposure Limits (RELs). RELs are authoritative federal agency recommendations established according to the legislative mandate for NIOSH to recommend standards to OSHA. RELs are intended to limit exposure to hazardous substances in workplace air to protect worker health. In developing RELs and other recommendations to protect worker health, NIOSH evaluates all available medical, biological, engineering, chemical, and trade information relevant to the hazard. NIOSH transmits its recommendations to OSHA for use in developing legally enforceable standards. NIOSH also publishes its recommendations in publicly available sources such as the NIOSH Pocket Guide to Chemical Hazards, Criteria Documents, Current Intelligence Bulletins, Alerts, Special Hazard Reviews, Occupational Hazard Assessments, and Technical Guidelines (OSHA, 2017).

In Germany, the establishment of occupational exposure limits dates back more than a century with establishment of *maximum tolerable concentrations in the workplace*. Workplace maximum tolerable concentrations were established for both short-term and long-term exposure. From the work to derive maximum tolerable concentrations for irritant gases, such as phosgene and hydrocyanic acid, a basic dose response principle known as Haber's Law was found. Haber's Law states that identical products of exposure concentration (c) and time (t) will result in identical magnitudes of effect (Henschler, 1991). This expression of concentration, time, and toxicity is seen in the following equation:

$$c \times t = W = \text{const}$$

The German Maximale Arbeitsplatz-Konzentration (MAK) list was introduced in 1983. The MAK value is "the maximum permissible concentration of a chemical compound present in the air within a working area (as gas, vapor, particulate matter), which, according to current knowledge, generally does not impair the health of the employee nor cause undue annoyance. Under these conditions, exposure can be repeated and of long duration over a daily period of 8 hours, constituting an average work week of 40 hours (42 hours per week as averaged over four successive weeks for firms having four work shifts). Scientifically based criteria for health protection, rather than their technical or economic feasibility, are employed." MAK values are derived by the "DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area" exclusively on the basis of scientific arguments and are published in the List of MAK and BAT Values, which is issued annually (DFG, 2012). Since 2005, a new limit value concept in Germany was introduced with the German Hazardous Substances Ordinance (GefStoffV). The GefStoffV establishes health-based limits, called Workplace Exposure Limit (WEL) and biological limit (BGW). The current Technical Rules for Hazardous Substances (TRGS), particularly TRGS 900 "Occupational Exposure Limits" with status of 4 August 2010 and the TRGS 903 "Biological

limit values" as per December 2006 should therefore be applied in Germany. The MAK values were included in the ordinance. The terms *TLV* and *BAT value* will continue in Germany by the permanent Commission for the Investigation of Health Hazards of Chemical Compounds of the Deutsche Forschungsgemeinschaft used (DFG) (BAuA, 2006).

In the United Kingdom, the Health and Safety Executive (HSE) issues a legally binding list of approved WELs. By referencing this list, the Control of Substances Hazardous to Health Regulations of 2002 imposed requirements, which were originally gathered from the ACGIH TLV list. In 2007, the European Commission's second Directive on Indicative Occupational Exposure Limit Values (2006/15/EC) was implemented in Great Britain and Northern Ireland. On December 18, 2011, the European Commission's third Directive on Indicative Occupational Exposure Limit Values (2009/161/EU) was implemented in Great Britain and Northern Ireland. This Directive requires Member States of the European Union to introduce domestic occupational exposure limits for the substances listed in the Annex to the Directive. Additionally, the level of the domestic limit must take account of the Indicative Occupational Exposure Limit Value (IOELV). The Health and Safety Executive has approved new and revised WELs required to implement the third IOELV Directive (HSE, 2011).

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12 Federal Air and Water Regulations

Clean Air Act, Clean Water Act, and Safe Drinking Water Act

Alicia A. Taylor and M. Yusuf Khan

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There are broad and diverse legislations, regulations, and regulatory practices that concern the protection of people and wildlife from potential toxic hazards in the environment. More specifically, there is a body of regulations that focuses on the principal means of environmental exposure—air and water. This text describes current air regulations, water regulations, regulatory practices, and provides a larger environmental health context through briefly outlining international air and water treaties. Table 12.1 summarizes the principle air and water laws in the United States, some of which will be discussed in greater detail within this chapter.

TABLE 12.1
Federal Laws Related to Air and Water Exposure to Toxic Substances

Legislation	Agency	Area of Concern
Clean Air Act (1963, amended 1970, 1974, 1977, 1978, 1980, 1981, 1982, 1983, 1990, 1997)	EPA	Air pollutants
Clean Water Act (1972, amended 1977, 1978, 1987, 1988, 1990, 1992)	EPA	Water pollutants
Comprehensive Environmental Response, Compensation, and Liability Act (1981, amended 1986) (CERCLA)	EPA	Hazardous substances, pollutants, and contaminants
Federal Mine Safety and Health Act (1977)	DOL and NIOSH	Toxic substances in coal and other mines
Hazardous Materials Transportation Act (1975, amended 1990 and 1994)	DOE, DOT, FAA, FHWA, FRA, OSHA, EPA, and USCG	Transport of hazardous materials
Marine Protection, Research and Sanctuaries Act (1972, 14 amendments from 1974 to 1992)	EPA	Ocean dumping
Oil Pollution Act (1990)	DOT	Oil pollution
Pollution Prevention Act (1990)	EPA	Toxics use reduction
Safe Drinking Water Act (1974, amended 1977, 1986, 1996, 2005, 2011, 2015)	EPA	Drinking water, contaminants

DOE = Department of Energy, DOL = Department of Labor, DOT = Department of Transportation, FAA = Federal Aviation Administration, FHWA = Federal Highway Administration, FRA = Federal Railroad Administration, NIOSH = The National Institute for Occupational Safety and Health, OSHA = Occupational Safety and Health Administration, EPA = Environmental Protection Agency, USCG = United States Coast Guard.

AIR REGULATIONS

In October 1948, a thick cloud of air pollution lingered for five days over the industrial town of Donora, Pennsylvania. This was a historic smog event that killed 20 people and sickened 6,000 out of the population of 14,000 people. Similarly, the great smog of London, or famously known as *killer smog*, was a severe air pollution event in December 1952, which killed 4,000 people in just four days.

Such events alerted citizens and officials about the danger that air pollution poses to public health and pushed Congress to establish and continually update the current regulations for controlling air pollution. In the United States, the original Clean Air Act (CAA) of 1963 was established to clean up air pollution and provide funds for research. However, even with the passing of the CAA, the federal government did not have a concrete plan to tackle air pollution and therefore, in 1970, Congress passed a much stronger CAA. In 1970, Congress also formed the US Environmental Protection Agency (EPA), giving the EPA the primary role to carry out environmental regulations. Since then, in 1977 and 1990, the EPA has made major revisions to the CAA to improve its effectiveness and to target newly recognized air pollution problems, such as acid rain and damage to the stratospheric ozone layer. The 1990 revision also gave more authority to the EPA for implementing and enforcing regulations for reducing air pollutant emissions, and emphasized more cost-effective approaches to reduce air pollution.

The CAA, like other laws enacted by Congress, was incorporated into the United States Code as Title 42, Chapter 85. The current version of the US code that includes the CAA changes enacted since 1990 is maintained by the House of Representatives.

CLEAN AIR ACT

- *Title*: Clean Air Act (CAA, 1963)
- *Agency*: EPA
- *Year passed*: 1963; amended 1970, 1974, 1977, 1978, 1980, 1981, 1982, 1983, 1990, and 1997
- *Groups regulated*: State and local governments, individuals, businesses, and non-profits

Synopsis of Law

The CAA requires the EPA to establish and update National Ambient Air Quality Standards (NAAQS) for six common pollutants found throughout the United States (Table 12.2). These criteria pollutants are particulate matter (PM), photo-chemicals and ground-level ozone, carbon monoxide (CO), sulfur oxides (SO_x), nitrogen oxides (NO_x), and lead. The NAAQS standards are required to be adopted by the states in order to maintain air quality and control emissions that might drift across state lines and harm air quality in downwind states. Another key element of the law is to control emissions from mobile and stationary sources such as motor vehicles and power plants, respectively. The law has provisions for new pollution sources to be controlled with the best available technology, whereas, in case of existing sources, less stringent standards are implemented.

The Clean Air Act Table of Contents by Title are:

- *Title I*: Air Pollution Prevention and Control
- *Part A*: Air Quality and Emissions Limitations (CAA § 101–131; USC § 7401–7431)
- *Part B*: Ozone Protection (replaced by Title VI)
- *Part C*: Prevention of Significant Deterioration of Air Quality (CAA § 160–169b; USC § 7470–7492)
- *Part D*: Plan Requirements for Nonattainment Areas (CAA § 171–193; USC § 7501–7515)

TABLE 12.2
EPA 2016 National Ambient Air Quality Standards

Air Pollutant	Primary Standard	Secondary Standard
Particulate matter (<10 μm)		
24-hour average	150 μg/m^3	150 μg/m^3
Particulate matter (<2.5 μm)		
24-hour average	35 μg/m^3	35 μg/m^3
Sulfur dioxide		
24-hour average	0.075 ppm	
3-hour average		0.5 ppm
Carbon monoxide		
8-hour average	9 ppm	No standard
1-hour average	35 ppm	No standard
Nitrogen dioxide		
Annual mean (arithmetic)	0.053 ppm	0.053 ppm
Ozone		
Maximum daily 8-hour average	0.070 ppm	0.070 ppm
Lead		
Maximum quarterly average	0.15 μg/m^3	0.15 μg/m^3

ppm: Parts per million; equivalent to mg/L.

- *Title II*: Emission Standards for Moving Sources
- *Part A*: Motor Vehicle Emission and Fuel Standards (CAA § 201–219; USC § 7521–7554)
- *Part B*: Aircraft Emission Standards (CAA § 231–234; USC § 7571–7574)
- *Part C*: Clean Fuel Vehicles (CAA § 241–250; USC § 7581–7590)
- *Title III*: General (CAA § 301–328; USC § 7601–7627)
- *Title IV*: Noise Pollution (USC § 7641–7642)
- *Title IV-A*: Acid Deposition Control (CAA § 401–416; USC § 7651–7651o)
- *Title V*: Permits (CAA § 501–507; USC § 7661–7661f)
- *Title VI*: Stratospheric Ozone Protection (CAA § 601–618; USC § 7671–7671q)

CLEAN AIR ACT TITLE I AIR POLLUTION PREVENTION AND CONTROL

Part A: Air Quality and Emissions Limitations

The purpose of this section of the act is to protect and enhance the quality of the air resources of the US so as to promote public health, welfare, and the productive capacity of its population. The law encourages prevention of regional air pollution and encourages control programs. The act mandates air quality control regions, designated as attainment versus nonattainment. Nonattainment areas do not meet national standards for primary or secondary ambient air quality. Attainment areas currently meet the national standards for primary and secondary air quality. Primary standards are the set of limits for criteria pollutants (PM, ozone, NO_x, SO_x, carbon monoxide, and lead) based on human health, whereas secondary standards are the set of limits intended to prevent environmental and property damage.

Also covered in Part A are air quality criteria and control techniques, national primary and secondary ambient air quality standards, state implementation plans for achieving national primary and secondary ambient air quality standards, and performance standards for new stationary sources. This act provides a list of hazardous air pollutants, including, but not limited to, acetaldehyde, benzene, chloroform, phenols, naphthalene, lead compounds, and fine mineral fibers. The list is periodically reviewed and published with new pollutants, which present a threat to human health or to the environment or may present a threat through inhalation or other routes of exposure.

The remaining subchapters of Part A covers a list of certain unregulated pollutants (radioactive pollutants, cadmium, arsenic, and polycyclic organic matter), smokestack heights, state plan adequacy, and emissions estimates of carbon monoxide (CO), volatile organic compounds (VOCs), and NO_x from stationary area and mobile sources. The final subchapter in Part A focuses on land-use authority.

Part C: Prevention of Significant Deterioration of Air Quality

The CAA requires permits to build or add to major stationary sources of air pollution. This permitting process, known as New Source Review (NSR), applies to sources in areas that meet air quality standards and areas that are unclassifiable. Unclassifiable areas are those that cannot be classified as attainment or nonattainment based on the information available. This means that not enough information is available to classify an area as attainment or nonattainment. Permits in attainment or nonattainment areas are referred to as prevention of significant deterioration (PSD) permits, while permits for sources located in nonattainment areas are referred to as nonattainment area (NAA) permits.

The purpose of the PSD permit is to protect public health and welfare from any actual or potential adverse effect. It also serves the purpose to preserve, protect, and enhance the air quality in national parks, national wilderness areas, national monuments, national seashores, and other areas of special national or regional natural, recreational, scenic, or historic value. Another fundamental purpose of Part C is to prevent development of new nonattainment areas by ensuring economic growth is in accord with existing clean air.

Part D: Plan Requirements for Nonattainment Areas

When an area does not meet air quality standard for one of the NAAQS pollutants, it is designated as a nonattainment area. Under the Clean Air Act, states are required to submit a state implementation plan (SIP), which explains how the area will comply with NAAQS in nonattainment areas. The state will outline its approach for reducing pollutant levels in the air or any precursor pollutants. Precursor pollutants are those that can form another pollutant in the atmosphere. For example, VOCs, and NO_x are precursor pollutants for ozone. The general requirement is to reach attainment status as soon as possible, typically within five years, except for cases where up to ten years are allowed to reach attainment status based upon the availability and feasibility of pollution control measures.

The SIP must include an inventory of all pollutants, permits, control measures, means and techniques to reach standard qualifications, and contingency measures. The plan must be approved or revised if required for approval and specify whether local governments or the state will implement and enforce the various changes. Achieving attainment status makes a request for re-evaluation of the nonattainment area classification possible. The SIP must include a plan for maintenance of air quality.

This section of the act also includes additional provisions for the all six criteria pollutants.

CLEAN AIR ACT TITLE II EMISSIONS STANDARDS FOR MOVING SOURCES

Part A: Motor Vehicle Emission and Fuel Standards

This section covers state standards, state grants, prohibited acts, actions to restrain violations, and civil penalties. It contains emissions standards for new motor vehicles or new motor vehicle engines. Information on motor vehicle and motor vehicle engine compliance testing and certification is also available. Moreover, this section requires compliance by vehicles and engines in actual use. Other subsections provide information on non-road engines and vehicles, high altitude performance adjustments and study of particulate emissions from motor vehicles.

This act provides detailed information on the regulation of the fuel, renewable fuels and on the prohibition on production of engines requiring leaded gasoline.

Part B: Aircraft Emission Standards

Aircraft engines are known for producing noise and air pollution. The exhaust from an aircraft engine includes carbon dioxide (CO) and criteria pollutants such as NO_x, SO_x, carbon monoxide, and PM. The major concern regarding airplane pollution is greenhouse gas (GHG) emissions and their implication in climate change. Aircrafts are the third largest contributor to GHG emissions in the United States transportation sector. Recently under the CAA, the EPA finalized a determination that GHG emissions, such as carbon dioxide, methane, nitrous oxide, hydrofluorocarbons (HFC), perfluorocarbons (PFC), and sulfur hexafluoride (SF_6), represent the largest driver for human-caused climate change.

This section sets emission standards for airlines and aircraft engines and adopts standards set by the International Civil Aviation Organization (ICAO). The subsection of this part also provides information on the enforcement of standards.

Part C: Clean Fuel Vehicles

In 2010, the EPA estimated that approximately 126 million people in the United States live in nonattainment areas. The Nonattainment areas listed were out of limits developed for at least one of the NAAQS. Passenger vehicles and heavy-duty trucks are the main sources of air pollution in these areas and specifically contribute to ozone, particulate matter, and other smog-forming emissions.

Passenger vehicles are a major pollution contributor, producing significant amounts of nitrogen oxides (NO_x), carbon monoxide (CO), and other pollution. In 2013, transportation contributed more than half of the carbon monoxide and NO_x, and almost a quarter of the hydrocarbons emitted into our air.

The health risks associated with outdoor air pollution are extremely serious. Ground-level ozone aggravates respiratory diseases, such as emphysema, bronchitis, and asthma. Particulate matter emitted from engines is directly linked to health problems. Small particles (less than 2.5 micrometer) can get deep into the lungs and may even enter the bloodstream, affecting both the lungs and heart. Particulate matter and ground level ozone emitted from road transportation are responsible for ~53,000 and ~5,000 premature deaths in 2005, respectively (Caiazzo et al., 2013).

The Clean Fuel Vehicle program encourages the use of alternative fuels and the development of cleaner engines. A clean fuel vehicle is one that meets Low Emission Vehicles (LEVs) standards specified in this section of the act. LEVs operate on reformulated gasoline, liquefied petroleum gas, natural gas, ethanol, methanol, reformulated diesel, or electricity. Moreover, California's Zero Emission Vehicle (ZEV) program is intended to promote the use of alternative fuels and more efficient engines.

This part of the act also provides standards for heavy-duty clean fuel vehicles and provisions for converting existing and new conventional vehicles to clean-fuel vehicles. The California pilot program incorporated under this section focuses on demonstrating the effectiveness of clean-fuel vehicles in ozone nonattainment areas. This provision of this section only applies to light-duty trucks and vehicles and only for the state of California, except for cases where other states voluntary opt in.

CLEAN AIR ACT TITLE III GENERAL PROVISIONS

Toxic air pollutants are defined as the pollutants hazardous to human health or the environment. The 189 toxic air pollutants listed by the EPA, which are not covered under other portions of the CAA, are responsible for causing 1,000–3,000 cancer-related deaths per year. The CAA amendment of 1990 outlines a comprehensive plan for achieving significant reductions in hazardous air pollutants from major sources. Title III also establishes a Chemical Safety Board to investigate the accidental release of chemicals. Moreover, it also requires the EPA to issue regulations controlling air pollution from hospital, municipal, and other commercial and industrial incinerators.

CLEAN AIR ACT TITLE IV NOISE POLLUTION

Unwanted or disturbing sound is defined as noise pollution. Sound becomes unwanted or disturbing when it either interferes with normal activities such as conversation, sleeping, or disrupts or diminishes one's quality of life.

Noise pollution adversely affects the lives of millions of people. Research has shown that there is a direct correlation between noise and human health. The most common health effect is Noise Induced Hearing Loss (NIHL). Health issues, such as stress related illnesses, high blood pressure, speech interference, hearing loss, sleep disruption, and lost productivity, are also associated with noise pollution.

Prior to 1981, the EPA administrator established the Office of Noise Abatement and Control (ONAC) to carry out investigations and study noise and its effect on public health and welfare. However, in 1981 the EPA concluded that state and local governments can best handle noise issues. As a result, ONAC was closed but the EPA still retains the authority to investigate and study noise and its effect, disseminate information to the public regarding noise pollution and its adverse health effects, respond to inquiries on matters related to noise, and evaluate the effectiveness of existing regulations for protecting the public health and welfare, pursuant to the Noise Control Act of 1972 and the Quiet Communities Act of 1978. (EPA, Clean Air Act Overview).

CLEAN AIR ACT TITLE IV-A ACID DEPOSITION CONTROL

The purpose of this subchapter is to reduce the adverse effects of acid deposition through reductions in the annual emission of sulfur dioxide (SO_2) from the ten million emitted tons measured in 1980, and, in combination with other provisions of this chapter, reduce nitrogen oxides emissions from approximately two million tons measured in 1980 emission levels, in the forty-eight contiguous states and the District of Columbia. Sulfur oxide (SO_x) reductions were planned using a two-step process. The first stage reduced SO_2 emission by about 3.5 million tons from facilities larger than 100 megawatts by January 1995. The second stage gave a deadline of January 2000 for facilities larger than 75 megawatts. The purpose of this subchapter was also to encourage energy conservation, use of renewable and clean alternative technologies, and pollution prevention as a long-range strategy, for the overall goal of reducing air pollution and other adverse impacts stemming from energy production and use.

CLEAN AIR ACT TITLE V PERMITS

Title V of the Clean Air Act requires major sources of air pollutants and certain other sources to obtain and operate in compliance with an operating permit. Sources with *Title V Permits* are required by the CAA to certify compliance with the applicable requirements of their permits at least annually.

CLEAN AIR ACT TITLE VI STRATOSPHERIC OZONE PROTECTION

Title VI of the 1990 CAA amendment enlists provisions for protecting the ozone layer. This amendment requires the EPA to develop and implement regulations for managing ozone-depleting substances (ODS) in the United States. It also implements the United States' international responsibilities under the Montreal Protocol on ODS. Since 1990, ODS such as CFCs (chlorofluorocarbons), methyl chloroform, carbon tetrachloride, and halons (Class I substances) have been phased out by the United States and other countries. Class II substances such as hydrochlorofluorocarbons (HCFCs) are banned starting in 2015, unless the HCFCs are used in feedstock, recycled, or are used as a refrigerant for appliances manufactured prior to January 1, 2020. Production of HCFCs are to be phased out by 2030.

If any substance has an ozone depletion potential (ODP) of 0.2 or greater, the EPA adds this substance to the list of Class I substances and sets requirements to phase out the substance in no more than seven years. For example, methyl bromide (ODP of 0.7) was phased out in 2001 after being added to the list in December 1993. Similarly, any substance that is known or may be reasonably anticipated to harm the stratosphere should be added to the list of Class II substances and should be phased out in less than ten years.

Title VI establishes methods for preventing harmful chemicals from entering the stratosphere in recycling (safe disposal) and emissions reduction program. It also establishes standards and requirements regarding the servicing of motor vehicles air conditioners. This section also promulgates regulations to implement the labeling requirements.

WATER REGULATIONS

Clean Water Act

- *Title*: CWA
- *Agency*: EPA
- *Years passed*: 1972; amended 1977–1983, 1987, 1988, 1990, 1992; reauthorized in 1997; originally the Federal Water Pollution Control Act of 1948
- *Groups regulated*: Industry

The Clean Water Act (CWA) is a US legislation; a 1972 re-write of the earlier Federal Water Pollution Control Act of 1948 (FWPCA, 1972). The objective of this act is to restore and maintain the chemical, physical, and biological integrity of United States waters. It is administered by the EPA. The EPA's main purpose is to authorize the regulation of emissions into water from municipal and industrial sources. In addition, the CWA provides funding for municipal sewage treatment plants. An example of an important action taken under this law includes setting standards for emissions of organic compounds from smelter operations. The provisions of the act are as follows:

- To eliminate the discharge of pollutants into navigable waters
- To achieve an interim goal of water quality for the protection and propagation of fish, shellfish, and wildlife
- To prohibit the discharge of toxic pollutants in toxic amounts
- To develop and implement waste treatment processes for adequate control of sources of pollutants
- To provide federal financial assistance to construct publicly owned waste treatment works
- To develop the technology necessary to eliminate the discharge of pollutants into navigable waters and the oceans

Synopsis of Law

The EPA has had responsibility for regulating toxic pollutants in water since 1972. As originally enacted, Section 307 of the CWA requires the EPA to develop and periodically update a list of toxic pollutants for which effluent standards (discharge limits) would then be established. The Toxic Pollutant List and the Priority Pollutant List have been developed from the CWA. Section 307 (a)(4) of the CWA specifies that the EPA, when establishing standards for any listed toxic pollutant, must provide an *ample margin of safety* that would prevent negative effects to public health caused by the pollutant. The law also mandates a rapid timetable and procedure for creating standards for each listed pollutant. The compounds in Table 12.3 are currently regulated under the Toxic Pollutant List. The CWA allows the federal government to recover clean-up costs and other costs as damages from the polluting agency, company, or individual. Additionally, the EPA can act under other provisions of the CWA to allow consideration of economic costs and technological feasibility in setting pollutant limits; this change to the CWA occurred during the 1977 amendment.

In 1987, Congress again amended the CWA to toughen standards for toxic pollutants. Under the 1977 amendment, the EPA developed health-based *water quality criteria* for 126 compounds identified as toxic. These criteria set, when possible, numerical concentration levels below thresholds associated with acute or chronic toxicity effects per each pollutant. Because the EPA's discharge limits are based upon best practicable control technologies, the water quality criteria are generally lower than the allowed pollutant concentration levels found in treated effluents from municipalities and industries (Heineck, 1989). The 1987 amendment required that these advisory water quality criteria created from the 1977 amendment must be incorporated by states into the state-level mandatory standards for water quality. Additionally, the 1987 amendment imposed additional effluent limitations on operations discharging into below-standard waterways.

Recent Supreme Court Modifications to the Clean Water Act

From 1990 through the 2000s, many lawsuits arose regarding implementation of the CWA. In particular, four rulings (mentioned in more detail in the following) have altered the way in which the CWA is defined and implemented by regulatory agencies. For example, in 2001 the Supreme Court decision in the Solid Waste Agency of Northern Cook County (SWANCC) v. US Army Corps of Engineers (Army Corps) resulted in the *SWANCC* decision, which eliminated CWA jurisdiction over discharge permits for non-navigable, intra-state, isolated waters. This ruling potentially removed some wetlands and waters from CWA jurisdiction, leaving these waters to be protected at

TABLE 12.3
Toxic Pollutants Regulated by the Clean Water Act[a]

Inorganics

Antimony and compounds
Arsenic and compounds
Asbestos
Beryllium and compounds
Cadmium and compounds
Chromium and compounds
Copper and compounds
Cyanides
Lead and compounds
Mercury and compounds
Nickel and compounds
Selenium and compounds
Silver and compounds
Thallium and compounds
Zinc and compounds

Organics

Acenaphthene
Acrolein
Acrylonitrile
Aldrin/dieldrin
Benzene
Benzidine
Carbon tetrachloride
Chlordane (technical mixture and metabolites)
Chlorinated benzenes (other than dichlorobenzenes)
Chlorinated ethanes (including 1,2-dichloroethane, 1,1,1-trichloroethane, and hexachloroethane)
Chloroalkyl ethers (chloroethyl and mixed ethers)
Chlorinated naphthalene
Chlorinated phenols (trichlorophenols and chlorinated cresols)
Chloroform
2-Chlorophenol
DDT and metabolites
Dichlorobenzenes (1,2-, 1,3-, and 1,4-dichlorobenzenes)
Dichlorobenzidine
Dichloroehtylenes (1,1- and 1,2-dichloroethylene)
2,4-Dichlorophenol
Dichloropropane and dichloropropene
2,4-Dimethylphenol
Dinitroltoluene
Diphenylhydrazine
Endosulfan and metabolites
Endrin and metabolites
Ethylbenzene
Fluoranthene
Haloethers [chlorophenylphenyl ether
bromophenylphenyl ether
bis(dichloroisopropyl)ether

(*Continued*)

TABLE 12.3 (*Continued*)
Toxic Pollutants Regulated by the Clean Water Act

Organics
bis(chloroethoxy)methane
polychlorinated diphenyl ethers]
Halomethanes (methylene chloride, methyl chloride, methyl bromide, bromoform, dichlorobromomethane)
Heptachlor and metabolites
Hexachlorobutadiene
Hexachlorocyclohexane
Hexachlorocyclopentadiene
Isophorone
Naphthalene
Nitrobenzene
Nitrophenols (2,4-dinitrophenol and dinitrocresol)
Nitrosamines
Pentachlorophenol
Phenol
Phthalate esters
Polychlorinated biphenyls (PCBs)
Polynuclear aromatic hydrocarbons (benzanthracenes, benzopyrenes, benzofluoranthene, chrysenes, dibenz-anthracenes, and indenopyrenes)
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
Tetrachloroethylene
Toluene
Toxaphene
Trichloroethylene
Vinyl chloride

[a] Toxic pollutants regulated by CWA Toxic Pollutant List in section 307(a)(1); 33 U.S.C. 1317(a). The Toxic Pollutant List is found in 40 CFR 401.15.

the state or local levels. The 2006 Rapanos v. United States ruling, considered important but largely unclear, resulted in the *significant nexus* test in which a water body is determined to be under CWA jurisdiction if it is deemed to have a significant connection with or impact to navigable waters. This ruling potentially eliminated CWA jurisdiction over waters that are ephemeral or adjacent to, but not connected with, navigable waters. In the 2012 Sackett v. US Environmental Protection Agency ruling (Chantell Sackett, et vir, Petitioners v. Environmental Protection Agency et al., 566 US [2012]), EPA compliance orders, documents that are issued to a party thought to be violating the CWA, were ruled eligible for immediate judicial review. This meant that compliance orders issued by the EPA may qualify for judicial review, determining whether the compliance order is legal. In the 2016 case of US Army Corps of Engineers v. Hawkes Co., Inc., the Supreme Court Justices ruled that wetland delineation is also subject to court review. Wetland delineation is the jurisdictional determination conducted by the Army Corps to assess if a body of water is governable under the CWA.

Safe Drinking Water Act

- *Title*: SDWA
- *Agency*: EPA
- *Year passed*: 1974; amended 1986, 1996, 2005, 2011, 2015
- *Groups regulated*: Water suppliers

The SDWA is a US drinking water act that sets standards for public health protection. It authorizes research relating to causes, diagnosis, treatment, control, and prevention of human diseases and other impairments resulting, directly or indirectly, from contaminants in drinking water (SDWA, 1974).

Synopsis of Law

The 1974 SDWA was enacted to ensure that public water supply systems "meet minimum national standards for the protection of public health." Under the SDWA, the EPA is required to regulate any contaminants in public drinking water supplies, "which may have an adverse effect on human health" (Douglas, 1976). The law, and its 1986 and 1996 amendments, protects drinking water derived from both public water systems and public drinking water sources, such as reservoirs, springs, ground-water wells, lakes, and rivers. To ensure safe drinking water is met under the SDWA, the EPA established national primary drinking water regulations (NPDWRs) for contaminants that cause adverse public health effects. These standards reinforce consistent quality in public water systems across the nation.

The SDWA gives the EPA authority to set NPDWRs for safe drinking water in a three-step process. First, the EPA identifies contaminants that are found in drinking water at a frequency and level that could cause adverse public health outcomes. Contaminants are then selected for additional study and determined if regulation is needed. Second, the EPA sets a maximum contaminant level goal (MCLG) for contaminants that will be regulated. MCLGs are non-enforceable health goals and are developed to ensure the contaminant stays below a certain level in drinking water that has no expected or known health risks. Essentially, MCLGs provide a margin of safety. Third, the EPA sets a maximum contaminant level (MCL) for each contaminant of concern. MCL is defined as the maximum permissible level of a contaminant in water, which is delivered to any user of a public water system. MCLs are enforceable standards and are set as close to the MCLGs as scientifically, technologically, and economically feasible using the best available treatment technologies. MCLs also include testing methods and requirements for water systems to ensure that the standards are met. MCLs are developed for six contaminant groups: microorganisms, disinfectants, disinfection byproducts, inorganic chemicals, organic chemicals, and radionuclides. The EPA has issued MCLs for contaminants in each of these groups. Table 12.4 lists the MCL and MCLG values of the currently regulated contaminants under the SDWA (EPA, 2009); it should be noted that some of the compounds listed are known carcinogens.

In addition, the EPA has authority under the SWDA to identify and list currently unregulated contaminants, which may need regulation and are known or anticipated to be found in public water systems. This list is publishable every five years and is called the Contaminant Candidate List. The list is a means for the EPA to identify priority contaminants, based on health effects and occurrence, which may need further information collected so that a regulatory decision can be made. After evaluation of data, the EPA can decide on whether these priority contaminants should be regulated under the NPDWRs.

Under the SDWA, the EPA also has authority to provide assistance, guidance, and information regarding public drinking water. The EPA collects data on drinking water and oversees all state drinking water programs. Because the United States has a variety of public water systems, the NPDWRs developed from the SDWA are applied differently based on size and type of the public water system (EPA, 2004). The EPA must work together with state and municipal water systems to ensure the SDWA standards are met.

For the SDWA to continue enforcement of drinking water standards, multiple amendments have been added that enhance the SDWA. The 1996 amendment expanded the scope of the SDWA by adding regulations that require the following: protecting source waters, increasing and/or updating operator training, delivering consumer reports for public right-to-know, conducting cost-benefit analyses for new contaminant standards, strengthening protection regarding microbial contaminants and disinfection byproducts, assisting small water systems, and funding water system infrastructure improvements. The 2005 amendment set regulatory limitations by excluding underground fluid

TABLE 12.4
National Primary Drinking Water Regulations

Inorganic Contaminants	MCL (mg/L)	MCLG (mg/L)
Antimony	0.006	0.006
Arsenic	0.01	0
Asbestos (fibers > 10 μm length)	7 MFL[a]	7 MFL
Barium	2	2
Beryllium	0.004	0.004
Cadmium	0.005	0.005
Chromium, total	0.1	0.1
Copper	1.3[b]	1.3
Cyanide	0.2	0.2
Fluoride	4	4
Lead	0.015[b]	0
Mercury (inorganic)	0.002	0.002
Nitrate (as N)	10	10
Nitrite (as N)	1	1
Selenium	0.05	0.05
Thallium	0.002	0.0005
Disinfectants[c]	**MRDL**	**MRDLG**
Chloramines (as Cl_2)	4	4
Chlorine (as Cl_2)	4	4
Chlorine dioxide (as ClO_2)	0.8	0.8
Organic Contaminants	**MCL (mg/L)**	**MCLG (mg/L)**
Acrylamide	TT[d]	0
Alachlor	0.002	0
Atrazine	0.003	0.003
Benzene	0.005	0
Benzo(a)pyrene (PAHs)	0.0002	0
Carbofuran	0.04	0.04
Carbon tetrachloride	0.005	0
Chlordane	0.002	0
Chlorobenzene	0.1	0.1
2,4-D	0.07	0.07
Dalapon	0.2	0.2
1,2-Dibromo-3-chloropropane (DBCP)	0.0002	0
o-Dichlorobenzene	0.6	0.6
p-Dichlorobenzene	0.075	0.075
1,2-Dichloroethane	0.005	0
1,1-Dichloroethylene	0.007	0.007
cis-1,2-Dichloroethylene	0.07	0.07
trans-1,2-Dichloroethylene	0.1	0.1
Dichloromethane	0.005	0
1,2-Dichloropropane	0.005	0
Di(2-ethyhexyl) adipate	0.4	0.4
Di(2-ethylhexyl) phthalate	0.006	0
Dinoseb	0.007	0.007

(*Continued*)

TABLE 12.4 (*Continued*)
National Primary Drinking Water Regulations

Organic Contaminants	MCL (mg/L)	MCLG (mg/L)
Dioxin (2,3,7,8-TCDD)	0.00000003	0
Diquat	0.02	0.02
Endothall	0.1	0.1
Endrin	0.002	0.002
Epichlorohydrin	TT[d]	0
Ethylbenzene	0.7	0.7
Ethylene dibromide	0.00005	0
Glyphosate	0.7	0.7
Heptachlor	0.0004	0
Heptachlor epoxide	0.0002	0
Hexachlorobenzene	0.001	0
Hexachlorocyclopentadiene	0.05	0.05
Lindane	0.0002	0.0002
Methoxychlor	0.04	0.04
Oxamyl (Vydate)	0.2	0.2
Pentachlorophenol	0.001	0
Picloram	0.5	0.5
Polychlorinated biphenyls (PCBs)	0.0005	0
Simazine	0.004	0.004
Styrene	0.1	0.1
Tetrachloroethylene	0.005	0
Toluene	1	1
Toxaphene	0.003	0
2,4,5-TP (Silvex)	0.05	0.05
1,2,4-Trichlorobenzene	0.07	0.07
1,1,1-Trichloroethane	0.2	0.2
1,1,2-Trichloroethane	0.005	0.003
Trichloroethylene	0.005	0
Vinyl chloride	0.002	0
Xylenes (total)	10	10
Disinfection Byproducts	**MCL (mg/L)**	**MCLG (mg/L)**
Bromate	0.01	0
Chlorite	1	0.8
Haloacetic acids (HAA5)	0.06	N/a[e]
Total trihalomethanes (TTHMs)	0.08	N/a[e]
Microorganisms	**MCL (mg/L)**	**MCLG (mg/L)**
Cryptosporidium	TT[f]	0
Fecal coliforms and *Escherichia coli*	TT[f]	0[g]
Giardia lamblia	TT[f]	0
Heterotrophic plate count (HPC)	TT[f]	N/a
Legionella	TT[f]	0
Total coliforms	5.0%[h]	0
Turbidity	TT[f]	N/a
Viruses (enteric)	TT[f]	0

(*Continued*)

TABLE 12.4 (*Continued*)
National Primary Drinking Water Regulations

Radionuclides	MCL (mg/L)	MCLG (mg/L)
Alpha/photon emitters	15 picocuries per Liter (pCi/L)	0
Beta photon emitters	4 millirems per year	0
Radium 226 and radium 228 (combined)	5 pCi/L	0
Uranium	30 μg/L	0

Source: EPA Proposed interim primary drinking water regulations and Environmental Protection Agency, 1978, *Fed. Reg.,* 43(130), 29135–29137 (to be codified at 40 C.F.R. § 141); EPA, NPDWR Alphabetical list of national primary drinking water regulations, EPA 816-F-09-004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf.

Note: EPA. May 2009. NPDWR Alphabetical list of national primary drinking water regulations. EPA 816-F-09-004.

Definitions: MCL is maximum contaminant level. MCLG is maximum contaminant level goal. TT is treatment technology.

[a] MFL defined as million fibers per liter.

[b] Copper and lead are regulated by a treatment technique requiring water systems to control water corrosivity.

[c] Regulated as maximum residual disinfectant level (MRDL) and maximum residual disinfectant level goal (MRDLG).

[d] Use of these compounds for drinking water treatment must not exceed set limits.

[e] As a group, these do not have numerical MCLGs, but individual compounds with these groups may have MCLGs.

[f] Additional EPA surface water treatment rules must be met.

[g] The testing method requires repeat samples to be taken if routine samples test positive for fecal coliforms and/or *Escherichia coli*.

[h] No more than 5% of samples can test positive in one month.

injections from SDWA regulation unless drinking water sources are affected. The 2011 amendment (Reduction of Lead in Drinking Water Act) tightens regulation on lead in drinking water by adding a rule to increase the use of lead-free materials in plumbing. Two amendments were added in 2015. First, The Drinking Water Protection Act (2015) requires the EPA to provide Congress with a plan for evaluating and managing algal toxin risks. The second amendment, titled The Grassroots Rural and Small Community Water Systems Assistance Act, gives technical support to small water systems to meet NPDWRs.

To further guide drinking water regulations, the SDWA also has national secondary drinking water regulations; these are unenforceable federal guidelines regarding aesthetic effects (e.g., taste, odor, or color) and cosmetic effects (i.e., tooth or skin discoloration) of drinking water. Secondary Maximum Contaminant Levels (SMCLs) are presented in Table 12.5. Federal law does not require water systems to comply with the secondary regulations, although they are recommended. States can adopt the secondary regulations as enforceable standards. For further information regarding drinking water regulations and *health advisories* readers may call the Safe Drinking Water Hotline at 1-800-426-4791 or US EPA's Office of Water at +1-202-564-5700.

COMPARISON TO WORLDWIDE REGULATIONS

It is important to note that there are multinational agreements for improving air and water quality. The Paris Agreement, developed within the United Nations Framework Convention on Climate Change (UNFCC), deals with greenhouse gas emissions and their mitigation. The Agreement was adopted in December 2015 and as of November 2016, has been signed by 193 UNFCC member counties and ratified by 100 member countries, with the Agreement going into effect on November 4, 2016. Also, numerous international treaties and projects exist regarding water. The United Nations

TABLE 12.5
National Secondary Drinking Water Standards

Contaminant	SMCL
Aluminum	0.05–0.2 mg/L
Chloride	250 mg/L
Color	15 color units
Copper	1 mg/L
Corrosivity	Noncorrosive
Fluoride	2 mg/L
Foaming agents	0.5 mg/L
Iron	0.3 mg/L
Manganese	0.05 mg/L
Odor	3 threshold odor number
PH	6.5–8.5
Silver	0.1 mg/L
Sulfate	250 mg/L
Total Dissolved Solids (TDS)	500 mg/L
Zinc	5 mg/L

Note: EPA. May 2009. NPDWR Alphabetical list of national primary drinking water regulations. EPA 816-F-09-004.
SMCL is secondary maximum contaminant level.

(UN) established a list of Sustainable Development Goals in 2015; one goal is to ensure access to clean water and sanitation for all people. The World Health Organization also provides guidelines for drinking water quality. The International Convention on the Control of Harmful Anti-Fouling Systems on Ships, a 2001 treaty developed by the International Maritime Organization, calls for a ban on paints containing harmful chemicals, which could negatively impact marine aquatic species and the environment.

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13 Understanding the Safe Drinking Water and Toxic Enforcement Act of 1986 (California's Proposition 65)

Clint Skinner

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THE ACT

The Safe Drinking Water and Toxic Enforcement Act of 1986, known as Proposition 65, became law in November 1986 when California voters approved it by a 63 to 37 percent margin. Proposition 65 was an initiative to lower exposure of the public to toxic chemicals. The act requires the State of California to publish a list of chemicals known to cause cancer or birth defects or other reproductive harm and to require a *clear and reasonable warning* wherever people might be exposed. The list is updated at least yearly and now includes over 900 chemicals. These chemicals include chemicals in household products, by-products of combustion, pesticides, food, drugs, dyes, solvents, and materials used in construction and manufacturing.

Prop 65 applies to all consumer goods sold within the state and impacts all importers, domestic manufacturers, and retailers of these items. Manufacturers and retailers that sell in California are

required to determine if their products require Proposition 65 labeling. Businesses with less than 10 employees (increased to 25 in 2013) and government agencies are exempt from Proposition 65's warning requirements and prohibition on discharges into drinking water sources.

The Proposition requires businesses to notify Californians if they release a significant amount of listed chemicals into the drinking water or the environment, or if the public may be exposed to these chemicals. The general warning states that the listed chemical is *known to the state to cause cancer or reproductive toxicity*, but it can be applied in various ways, including: labeling consumer products, posting signs at the workplace, distributing notices, and publishing notifications within newspapers. Businesses have 20 months to comply with the chemical discharge prohibition. Penalties for failing to provide notification can amount to as much as $2,500.00 per each violation, per day of violation. These warning requirements provide an incentive to remove listed chemicals from their products.

The Cal EPA Office of Environmental Health Hazard Assessment (OEHHA) administers the Proposition 65 program. OEHHA also evaluates all currently available scientific information on substances considered for placement on the Proposition 65 list. Information is available on their website: (OEHHA Proposition 65 Law and Regulations; Proposition 65 in Plain Language, in Refs.).

UPDATE TO THE PROPOSITION 65 ACT—MAY 20, 2016

In May 2013, California Governor Jerry Brown proposed: "to revamp Proposition 65 by ending frivolous *shake-down* lawsuits, improving how the public is warned about dangerous chemicals, and strengthening the scientific basis for warning levels." In response, on January 12, 2015, OEHHA formally released a draft of new Proposition 65 regulations. (Notice Of Modification To Text Of Proposed Regulation Title 27).

The amendments, which are set to take effect August 30, 2018, update the requirements for Prop 65 chemical warning labels, including a re-write of Section 25601, which lays out the criteria for what constitutes a *clear and reasonable* warning. Other critical changes in the Prop 65 amendments include redefining key terms like *label*, *sign*, *occupational exposure*, and other changes including:

1. Adding definitions for the terms *food*, *consumer information*, *knowingly*, and more
2. Revising criteria for determining responsibility to provide product warnings
3. Updating requirements for the content of consumer product exposure warnings
4. Changes to the current *safe harbor* warning

OTHER IMPORTANT SECTIONS INCLUDE

1. Section 25600(b) was modified to clarify that a warning that complies with Article 6 that is provided before the two-year effective date will be deemed to be clear and reasonable.
2. Section 25600.2(f) (formerly numbered as [e]) was modified to simplify the explanation of the notice requirement, and to allow five business days, rather than two, in response to stakeholder requests for an extension of the time period in which a retail seller is deemed to have *actual knowledge* of an exposure.
3. Section 25600.2(g) (formerly numbered as [f]) was modified to clarify that a retail seller must *promptly* provide the requested information; this change was made to require action on behalf of the retail seller in response to the request. The term *supplier* was also added for consistency.
4. Section 25601(c) was modified to clarify that any one of the listed chemicals for which the person has determined a warning is required can be included in the warning and that if the warning is for more than one endpoint, then one or more chemicals for each endpoint must be included in the warning unless the named chemical is listed for both endpoints. The phrase "to the extent an exposure to that chemical is at a level requiring a warning" was also removed in response to stakeholder comments.

5. A new subsection (d) was added to Section 25601 to clarify how a consumer product exposure warning must be provided. This provision was included in Section 25601 to provide safe harbor guidance regarding consumer product exposure warnings.
6. A new subsection (e) was added to Section 25601 to clarify how an environmental exposure warning must be provided. This provision was included in Section 25601 to provide guidance regarding safe harbor environmental product exposure warnings.
7. New subsection (f) to Section 25601 was moved from Section 25600(d) and modified to clarify the types of supplemental information that may be provided in a warning.
8. Section 25603(a)(2)(C) was modified to clarify situations in which a warning is required for multiple chemicals that each cause a different toxicity endpoint.
9. Section 25603(a)(2)(D) was added to clarify the situation in which a warning is required for a chemical that causes both toxicity endpoints.
10. In response to stakeholder comments concerning adequacy of the safe harbor environmental exposure provisions, Section 25604 was modified to more clearly state the requirements for transmitting an environmental exposure warning and clarifying that for indoor environments or outdoor spaces with clearly defined entrances, the specified warning method in subsection (a)(1) must be used.
11. Sections 25605(a)(3), (a)(4) and (a)(5) were modified to clarify that a description of the exposure source should be included in the warning.
12. Sections 25607.27(a)(3) and (b)(3) were modified to include an additional caution statement, "Do not stay in this area longer than necessary" in the warning. (OEHHA Side-by-Side Comparison of Old and New Prop 65 Text).

CHOOSING CHEMICALS FOR PROPOSITION 65

A chemical can be listed by either the Carcinogen Identification Committee (CIC) or the Developmental and Reproductive Toxicology (DART) Identification Committee. These groups are part of OEHHA's Science Advisory Board. The committee members are appointed by the Governor and are designated as the *State's Qualified Experts* for evaluating chemicals under Proposition 65.

When determining whether a chemical should be placed on the list, the committees base their decisions on the most current scientific information. First, OEHHA staff scientists compile all relevant scientific evidence on suspect chemicals for the committees to review. The committees also consider comments from the public and industry scientists before making their decisions.

A second way a chemical may be listed is if an *authoritative body*, designated by OEHHA, has identified it as causing cancer or reproductive harm. The following organizations have been designated as authoritative bodies: the US Environmental Protection Agency (US EPA), US Food and Drug Administration (US FDA), National Toxicology Program (NTP), National Institute for Occupational Safety and Health (NIOSH), and the International Agency for Research on Cancer (IARC).

A third way for a chemical to be listed is if an agency of the state or federal government requires labeling for risk of cancer, birth defects, or other reproductive harm. This mechanism is mostly limited to prescription drugs required by the FDA to contain label warnings.

A fourth way requires the listing of chemicals meeting certain scientific criteria and identified in the California Labor Code as causing cancer, birth defects, or other reproductive harm. The California Labor Code is a collection of civil law statutes, which govern the general obligations and rights of persons within the jurisdiction of the State of California. The code refers to listings by authoritative bodies such as IARC. This method established the initial chemical list following voter approval of Proposition 65 in 1986 and continues to be used as a basis for listing as appropriate.

THE LISTING PROCESS

1. OEHHA monitors publications from authoritative bodies and open literature to identify chemicals that Labor Code §6382(b)(1) or (d) appear to require to be listed.
2. OEHHA publishes a notice in the California Regulatory Notice Register of chemicals that appear to meet the listing criteria and invite comment during a 30-day public comment period.
3. OEHHA review comments to the notice of intent to list.
4. At least 45 days from date of notice of intent to list in California Regulatory Notice Register, if chemicals are still deemed to meet listing criteria, OEHHA publishes a Notice of Listing, revised Proposition 65 list, and provide responses to comments.
5. If the chemical does not meet listing criteria, OEHHA gives a notice of decision not to list and provides responses to comments. (OEHHA Proposition 65 in Plain Language, see refs.).

CHEMICALS IN THE PROPOSITION 65 LISTS

The following are lists of known human carcinogens, teratogens, and reproductive toxicants—as an important subset of the Proposition 65 list, which also contains chemicals listed based on animal data.

LIST OF KNOWN HUMAN CARCINOGENS—NATIONAL TOXICOLOGY PROGRAM AND INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

Known human carcinogens are agents that have caused tumors in man. They include: aflatoxins, alcoholic beverage consumption, 4-aminobiphenyl, phenacetin, aristolochic acids, arsenic, asbestos, azathioprine, benzene, benzidine, beryllium, bis (chloromethyl) ether, 1,3-butadiene, busulfan, cadmium, chlorambucil, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (meccnu), chromium hexavalent compounds, coal tars, coke oven emissions, cyclophosphamide, cyclosporin a, diethylstilbestrol (DES), benzidine, Epstein-Barr virus (EBV), erionite, estrogens, ethylene oxide, formaldehyde, hepatitis b & c virus, HIV-1 virus, human papilloma viruses (HPVs), HTLV-1 virus, herpes virus (KSHV), melphalan Merkel cell polyomavirus (mcv), methoxsalen with ultraviolet a therapy (puva), mineral oils (untreated and mildly treated), mustard gas, 2-naphthylamine, neutrons, nickel compounds, tobacco products, radon, silica, crystalline (respirable size), solar radiation, soots, sulfuric acid, sunlamps, tamoxifen, tetrachlorodibenzodioxin (TCDD), *dioxin*, thiotepa, thorium dioxide, o-toluidine, trichloroethylene (TCE), vinyl chloride, ultraviolet (UV) radiation, wood dust, x-radiation, and gamma radiation (ACS - See Refs.).

LIST OF KNOWN HUMAN TERATOGENS

Human teratogens include agents that can alter DNA, or normal processes of organ development, leading to birth defects in offspring. They include organic mercury, lead compounds, ionizing radiation, thalidomide, alcohol, nitrous oxide, diethylstilbestrol (DES), aminopterin, bisulfan, phenytoin, and methotrexate.

LIST OF KNOWN HUMAN REPRODUCTIVE TOXINS

Reproductive toxins are chemicals that can cause reproductive harm to the adults or developmental harm to offspring. They include aflatoxin B1, 1,2-dibromo-3-chloropropane (DBCP), 1,3-butadiene, dibromide, cadmium, mercury, boron, lead, chromium, bisphenol A, polychlorinated biphenyls,

carbon disulphide ethylene glycol ethers, enflurane, halothane, nitrous oxide, antineoplastic agents, chlordecone, ethanol (high dose), ethylene oxide, isocyanates, and vinyl chloride.

FOODSTUFF CONTAMINANTS LISTED BY PROPOSITION 65

Caramel coloring: Used in soft drinks, baked foods, and sauces. Some caramel coloring types have been listed as carcinogens due to 4-methylimidazole (4-MEI)—listed in 2011 as a carcinogen. 4-MEI is produced during the normal cooking process. It can also be generated when meats are roasted or grilled, in roasting coffee beans, and as a trace impurity when some types of caramel coloring are made (known as Class III and Class IV caramel coloring).

Aflatoxins (listed as carcinogens in 1988): Are naturally occurring mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus*; aflatoxin metabolites may be found in peanut butter due to fungal growth on shells and in milk of animals fed contaminated feed.

Ethyl alcohol in beverages: Ethanol with alcoholic use is listed as a reproductive toxicant since 1988.

Acrylamide (listed as a reproductive toxicant February 2011): Is one of the reasons Proposition 65 labels appear in California coffee shops. Acrylamide forms naturally in some foods during cooking, and it is present in bread, cereal, cookies, potato chips, and so on. However it has only been shown as carcinogenic at extremely high doses.

Mercury (listed as reproductive toxicant July 1990): Was litigated in 2001 against the canned tuna industry. The companies claimed that it is naturally occurring and below the Safe Harbor level. Due to Prop 65 and FDA advisories some large grocers have posted warnings.

Polycyclic aromatic hydrocarbons: 6 PAHs were listed by Prop 65. Listing occurred as follows: benzo[b]fluoranthene and benzo[j]fluoranthene on July 1, 1987; dibenzo[a, h]pyrene and dibenzo[a,i]pyrene on January 1, 1988; 5-methylchrysene on April 1, 1988; and chrysene on January 1, 1990—all listed as carcinogens. In 2006, veteran Proposition 65 plaintiffs filed lawsuits against numerous restaurant chains for failing to warn Californians that their flame-broiled and grilled meat products contained (PAHs) and PhIP (i.e., 2-Amino-1-Methyl-6-Phenylimidazol[4,5-B]Pyridine). PAHs are chemical compounds formed during the burning of coal, oil, gas, wood, and other organic substances. In meats, PAHs are formed when the fat drips onto a hot surface and the resulting smoke, which contains PAH, is deposited back into the food. PhIP, on the other hand, is formed directly in the meat as a result of grilling and broiling. While some of those Proposition 65 cases have settled out of court, other suits remain in active litigation.

(See OEHHA Proposition 65 List for all listed chemicals)

SAFE HARBOR AND *DE MINIMIS* CRITERIA

To help industry determine whether a warning is necessary or when discharges into drinking water is prohibited, OEHHA has developed safe harbor levels. A *safe harbor*, as defined by Proposition 65 warning requirements or discharge prohibitions, exists if exposure to the chemical is at or below *de minimis* or safe exposure levels. The safe harbor levels consist of (1) No Significant Risk Levels (NSRLs) for chemicals listed as carcinogens and (2) Maximum Allowable Dose Levels (MADLs) for chemicals listed as causing birth defects or reproductive harm. OEHHA has established over 300 safe harbor levels to date and continues to develop them. For chemicals listed as carcinogens,

the *no significant risk level* is defined as the level of exposure that would result in not more than one excess case of cancer in 100,000 individuals exposed to the chemical over a 70-year lifetime. For chemicals listed as causing reproductive harm, the *no observable effect level* is determined by dividing the No Observed Effect Level (NOEL) in humans or laboratory animals by 1,000 in order to provide an ample margin of safety. If exposure will be below these Safe Harbor levels, then the business is in a *Safe Harbor* versus the law.

Regulations concerning warnings are available at Article 7 and Article 8 of Title 27, California Code of Regulations as summarized in the following. Determining anticipated levels of exposure to listed chemicals can be very complex. Although a business has the burden of proving a warning is not required, a business is discouraged from providing a warning that is not necessary and instead should consider consulting a qualified professional if it believes an exposure to a listed chemical may not require a Proposition 65 warning.

DETERMINING NO SIGNIFICANT RISK LEVELS FOR CARCINOGENS

1. A quantitative risk assessment that conforms to this section shall be deemed to determine the level of exposure to a listed chemical, which, assuming daily exposure at that level, poses no significant risk. The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards, which form the scientific basis for listing the chemical as known to the state to cause cancer. In the absence of principles or assumptions scientifically more appropriate, based upon the available data, the following default principles and assumptions shall apply in any such assessment:
   a. Animal bioassay studies for quantitative risk assessment shall meet generally accepted scientific principles, including the thoroughness of experimental protocol, the degree to which dosing resembles the expected manner of human exposure, the temporal exposure pattern, the duration of study, the purity of test material, the number and size of exposed groups, the route of exposure, and the extent of tumor occurrence.
   b. The quality and suitability of available epidemiologic data shall be appraised to determine whether the study is appropriate as the basis of a quantitative risk assessment, considering such factors as the selection of the exposed and reference groups, reliable ascertainment of exposure, and completeness of follow-up. Biases and confounding factors shall be identified and quantified.
   c. Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality.
   d. The results obtained for the most sensitive study deemed to be of sufficient quality shall be applicable to all routes of exposure for which the results are relevant.
   e. The absence of a carcinogenic threshold dose shall be assumed, and no-threshold models shall be utilized. A linearized multistage model for extrapolation from high to low doses, with the upper 95% confidence limit of the linear term expressing the upper bound of potency shall be utilized. Time-to-tumor models may be appropriate where data are available on the time of appearance of individual tumors, and particularly when survival is poor due to competing toxicity.
   f. Human cancer potency shall be derived from data on human or animal cancer potency. Potency shall be expressed in reciprocal milligrams of chemical per kilogram of bodyweight per day. Interspecies conversion of animal cancer potency to human cancer potency shall be determined by multiplying by a scaling factor equivalent to the ratio of human to animal bodyweight, taken to the one-fourth power.
   g. When available data are of such quality that physiologic, pharmacokinetic, and metabolic considerations can be taken into account with confidence, they may be used in the risk assessment for inter-species, inter-dose, and inter-route extrapolations.

h. When the cancer risk applies to the general population, human body weight of 70 kilograms shall be assumed. When the cancer risk applies to a certain subpopulation, the following assumptions shall be made, as appropriate:

Subpopulation	Kilograms of Body Weight
Man (18+ years of age)	70
Woman (18+ years of age)	58
Woman with conceptus	58
Adolescent (11–18 years of age)	40
Child (2–10 years of age)	20
Infant (0–2 years of age)	10

2. For chemicals assessed in accordance with this section, the risk level which represents no significant risk shall be one that is calculated to result in one excess case of cancer in an exposed population of 100,000, assuming lifetime exposure at the level in question, except where sound considerations of public health support an alternative level.

DETERMINING MAXIMUM ALLOWABLE DOSE LEVELS (MADL) FOR REPRODUCTIVE TOXINS

For chemicals "known to the State to cause reproductive toxicity" as produced by OEHHA in the listing process, an exemption from the warning requirement is provided by the Act when a person in the course of doing business is able to demonstrate that an exposure for which he or she is responsible produces no observable reproductive effect, assuming exposure at 1,000 times the level in question (Health and Safety Code Sections 25249.10 and 25249.11). The maximum dose level at which a chemical has no observable reproductive effect is referred to as the no observed effect level (NOEL). The Act also provides an exemption from the prohibition against discharging a listed chemical into sources of drinking water if the amount discharged does not constitute a *significant amount*, as defined, and the discharge is in conformity with all other laws and regulatory requirements (Health and Safety Code sections 25249.9 and 25249.11). The term *significant amount* is defined in a manner that equates to the level that triggers the warning requirement. Thus, these exemptions apply when an exposure or discharge does not exceed the NOEL divided by 1,000.

The regulations provide three ways by which a person while doing business may make such a determination:

1. By conducting a risk assessment in accordance with the principles described in Section 12803 to derive a NOEL, and dividing the NOEL by 1,000; or
2. By application of the specific regulatory level adopted for the chemical in Section 12805; or
3. In the absence of such a level, by using a risk assessment conducted by a state or federal agency, provided that such assessment substantially complies with Section 12803(a). The specific regulatory levels in Section 12805 represent one one-thousandth (1/1000) of the NOEL. This proposed regulation sets forth no significant risk levels (NSRLs) for adoption into Section 12705(b) using scientific methods consistent with procedures outlined in Section 12703. This proposed regulation also sets forth maximum allowable dose levels (MADLs) for adoption into Section 12805 using scientific methods outlined in Section 12803. Details on the scientific basis for the proposed numbers are provided in the references cited in the following, which are also included in the rulemaking record. (California Code of Regulations Title 27, ARTICLE 7. No Significant Risk Levels).

CURRENT PROPOSITION 65 SAFE HARBOR VALUES

See references: Office of Environmental Health Hazard Assessment Proposition 65 No Significant Risk Levels (NSRLs) for Carcinogens and Maximum Allowable Dose Levels (MADLs) for Chemicals Causing Reproductive Toxicity. (OEHHA Proposition 65 Current No Significant Risk Levels).

ENFORCEMENT OF PROPOSITION 65

The California Attorney General's Office enforces Proposition 65. Any district attorney or city attorney (for cities whose population exceeds 750,000) may also enforce Proposition 65. In addition, any individual acting in the public interest may enforce Proposition 65 by filing a lawsuit against a business alleged to be in violation of this law. This leads to *bounty hunter* lawsuits. Lawsuits have been filed by the Attorney General's Office, district attorneys, consumer advocacy groups, private citizens, and law firms. Penalties for violating Proposition 65 by failing to provide notices can be as high as $2,500 per violation, per day. Lawsuits often end with a consent agreement where a business agrees to reformulate a product to remove or lower exposure to the safe harbor level to terminate the lawsuit. (OEHHA Proposition 65 in Plain Language).

CONCLUSION

Although Proposition 65 has clearly benefited Californians, it is considered a burden for some companies doing business in the state, and those who ship to California. Business are required to test products, develop alternatives to listed chemicals, reduce discharges, provide warnings, and pay for civil fines and legal defenses. Some businesses have posted generic warnings just in case their products contain listed chemicals. After 30 years, recent data issued by California's Attorney General suggest that more than 70% of the money exchanged under Prop 65 in court settlements goes to law firms. Unlike most laws, which are enforced by the state, this *bounty hunter* provision leads to legal costs for businesses beyond the state's civil penalties. As with other toxic torts, companies in full compliance with the law are sometimes forced to settle out of court to avoid trial costs and negative publicity. Small businesses often lack the resources to fight a case in court and are likely to settle out of court. They are also more likely to be unaware of the requirements for warnings and of impurities in their products. Bounty hunters are not required to prove injury, if individuals can find just one of the more than 900 chemicals in a place of business, they have grounds for a lawsuit.

Proponents of Proposition 65 point out that it provides Californians with information to reduce exposure to toxic chemicals. It has removed lead and cadmium in many commodities, acrylamide from foods, trichloroethylene from white-out, methylene chloride from paint strippers, toluene from nail care products, and DEHP (phthalate esters) from book covers and jackets. Proposition 65 has also succeeded in reducing California air emissions of listed chemicals, such as ethylene oxide, hexavalent chromium, and chloroform, and the law has led to increased awareness of the dangers of consuming alcohol during pregnancy. Relief for the burden on businesses is expected with the update to the law, which will take effect in 2018. Also, in 2013, California's legislature passed a law giving businesses with fewer than 25 employees, a 14-day window to put up Prop 65 signs, pay a $500 fine, and avoid a lawsuit.

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14 Safety Data Sheets

Dexter W. Sullivan, Jr.

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INTRODUCTION

Underpinning all hazard communication regulations around the world is the requirement that Safety Data Sheets (SDS), previously known as Material Safety Data Sheets (MSDSs), on hazardous chemicals are provided in the workplace and that hazardous chemicals are adequately labeled. These regulations also define, in elaborate detail, what makes a chemical hazardous and define many rules on how this information should be communicated on SDSs and labels.

The United States has been one of the world leaders for legislation and regulation on matters of workplace safety. A more detailed description of these regulations can be found in Chapter 11 of this book. The Occupational Safety and Health (OSH) Act of 1970 arose as a result of two decades of increasing concern about hazards in the workplace. It was soon realized that Occupational Safety and Health Administration (OSHA) could not possibly establish standards for every hazardous chemical; yet hazard information on each chemical used in the workplace was needed by every worker coming into contact with the chemical. In 1974, National Institute for Occupational Safety and Health (NIOSH) recommended label regulations and established a Standards Advisory Committee to develop a standard for hazard communication (DHEW, 1974; DOL, 1975). The Committee issued a report on June 6, 1975, recommending a comprehensive program of labels and other information reinforced by training programs.

The pace of voluntary action began to increase in the late 1970s. American National Standards Institute (ANSI) published voluntary hazard warnings and precautionary labeling guidelines in 1976. OSHA published a recommendation for a form to be used (OSHA Form 20) as an MSDS. An MSDS is a comprehensive document with information regarding safe use of a chemical. It includes a description of hazards, precautionary practices, protective equipment, first aid, and information to assist in spill clean-up and fire-fighting. Although providing MSDSs was only optional at the time, most major chemical companies began providing MSDSs because of increasing customer requests. Many chemical companies began to find that customers would not accept new chemicals without an MSDS or similar documents. After a decade of regulatory and legislative negotiating and lobbying, the OSHA Hazard Communication Standard became effective in 1985 as a regulation under the existing OSH Act without need of new legislation.

The regulatory history covering the control of workplace hazards has been similar amongst the major industrialized nations around the globe. Developed over the last 50 years, laws and regulations regarding hazard communication, transportation requirements, and the development of safe exposure limits will be described in this chapter.

HAZARD COMMUNICATION: BACKGROUND AND BASIC REQUIREMENTS FOR SAFETY DATA SHEETS

Hazard communication regulations usually specify a comprehensive set of requirements including worker training and the availability of information, such as SDSs, container labels, and lists of hazardous chemicals in the workplace. The regulations also specify in great detail the minimum content of SDSs and labels and the definitions of health and safety hazards. The main role of company-employed toxicologists is to write SDSs and labels evaluating the health hazards of the chemicals manufactured and sold as products. This is a complex task for companies, which sell their products internationally, since the requirements and definition of hazards can be quite different in various countries. As this chapter primarily focuses on the development of SDSs, the health hazard definitions of the various major international hazard communication requirements are presented in detail in Chapter 11 of this book.

Until recently, classification and labeling systems were developed separately by many countries. During the 1992 Rio de Janeiro United Nations Conference on Environment and Development (UNCED), it was decided to develop a single, Globally Harmonized System of Classification and Labeling of Chemicals (GHS) to replace all national schemes and address the classification of chemicals, labels, and safety data sheets (OECD, 2012). Development of the GHS began with three technical focal points. The Organization for Economic Cooperation and Development (OECD) focused on health and environmental hazards, the UN Committee of Experts on the Transport of Dangerous Goods (UNCETDG) in cooperation with the International Labor Organization (ILO) developed the system for physical hazards, and the ILO took the lead for hazard communication (van der Kolk, 2014). As part of the GHS, a standardized format was developed for SDSs. The GHS SDSs require a 16-heading format in a specific order. There was a great deal of international cooperation in the development of this standard. However, countries have flexibility to implement the GHS completely or partially as they see fit for their country's needs. Therefore, toxicologists and other members of companies' SDS writing teams need to pay close attention to these differences to assure their company's SDSs are acceptable in the countries where their chemicals are manufactured and their products are sold. The 16 sections specified by the GHS standards (UNECE, 2015) are given in Table 14.1 and further described in the following.

TABLE 14.1
Section Headings and Order Specified by the GHS Standard for SDSs (UNECE, 2015)

Section 1	Identification
Section 2	Hazard identification
Section 3	Composition/information on ingredients
Section 4	First-aid measures
Section 5	Fire-fighting measures
Section 6	Accidental release measures
Section 7	Handling and storage
Section 8	Exposure controls/personal protection
Section 9	Physical and chemical properties
Section 10	Stability and reactivity
Section 11	Toxicological information
Section 12	Ecological information
Section 13	Disposal considerations
Section 14	Transport information
Section 15	Regulatory information
Section 16	Other information

Identification

Section 1, the identification section of the SDS, should provide the name of the substance or mixture, recommended uses, and detailed contact information of the supplier including an emergency contact. The identity of the substance should be listed exactly as found on the label. Other means of identification including product codes, numbers, and all known synonyms should also be listed. Also included in the list should be the intended use of the substance or mixture, including a brief description of what it does, and any use restrictions.

Hazard Identification

Section 2 of the SDS describes the hazards of the substance or mixture, including the appropriate signal words, hazard classifications, hazard statements, and precautionary statements associated with those hazards. Hazard classifications are listed in this section when appropriate and include:

- Explosives or desensitized explosives
- Flammable gases
- Flammable or pressurized aerosols
- Oxidizing gases
- Gases under pressure
- Flammable liquids
- Flammable solids
- Self-reactive substances and mixtures
- Pyrophoric liquids or solids
- Self-heating substances and mixtures

- Substances and mixtures, which emit flammable gases when in contact with water
- Oxidizing liquids or solids
- Organic peroxides
- Corrosive to metals
- Acute toxicants
- Skin corrosion/irritants
- Eye irritants
- Respiratory sensitizers
- Skin sensitizers
- Mutagens
- Carcinogens
- Reproductive toxicants
- Target organ toxicants (single or repeat exposures)
- Aquatic environment hazards (acute or chronic)
- Ozone layer hazards

Hazard classifications should be accompanied with appropriate pictograms (or symbol name), signal words, hazard statements, and precautionary statements. GHS pictograms, along with their associated hazard class and category are provided in Table 14.2. Hazard statements are statements assigned to a hazard class and category that describes the nature of the hazards of a hazardous product, and where appropriate, the degree of the hazard (UNECE, 2015). Hazard statements are composed of an alphanumerical code consisting of the letter H (for hazard statement), a number designating a physical (1), health (2), or environmental (3) hazard, and a two-digit number corresponding to substance properties based on the hazards of the substance. A complete list of hazard statements is provided in Table 14.3.

Precautionary statements are phrases that describe recommended measures, which should be taken to minimize or prevent adverse effects resulting from exposures to a hazardous product or

TABLE 14.2
Pictograms and Associated Hazard Classifications Listed in Annex 1 of the GHS (UNECE, 2015)

 Exploding Bomb	Unstable explosives Explosives of Divisions 1.1, 1.2, 1.3, 1.4 Self-reactive substances and mixtures, types A, B Organic peroxides, types A, B
 Flame	Flammable gases, category 1 Pyrophoric gas Aerosols, categories 1, 2 Flammable liquids, categories 1, 2, 3 Flammable solids, categories 1, 2 Self-reactive substances and mixtures, types B, C, D, E, F Pyrophoric liquids, category 1 Pyrophoric solids, category 1 Self-heating substances and mixtures, category 1, 2 Substances and mixtures which in contact with water, emit flammable gases, categories 1, 2, 3 Organic peroxides, types C, D, E, F Desensitized explosives, categories 1, 2, 3, 4

(*Continued*)

TABLE 14.2 (*Continued*)
Pictograms and Associated Hazard Classifications Listed in Annex 1 of the GHS (UNECE, 2015)

Flame Over Circle

Oxidizing gases, category 1
Oxidizing liquids, categories 1, 2, 3
Oxidizing solids, categories 1, 2, 3

Gas Cylinder

Gases under pressure
- Compressed gas
- Liquefied gas
- Refrigerated liquefied gas
- Dissolved gas

Corrosion

Corrosive to metals, category 1
Skin corrosion/irritation, category 1
Serious eye damage/eye irritation, category 1

Skull and Crossbones

Acute toxicity (oral, dermal, inhalation), categories 1, 2, 3

Exclamation Mark

Acute toxicity (oral, dermal, inhalation), category 4
Skin corrosion/irritation, category 2
Serious eye damage/eye irritation, category 2/2A
Skin sensitization, categories 1, 1A, 1B
Specific target organ toxicity-single exposure, category 3
Hazardous to the ozone layer, category 1

Health Hazard

Respiratory sensitization, categories 1, 1A, 1B
Germ cell mutagenicity, categories 1A, 1B, 2
Carcinogenicity, categories 1A, 1B, 2
Reproductive toxicity, categories 1A, 1B, 2
Specific target organ toxicity-single exposure, categories 1, 2
Specific target organ toxicity-repeated exposure, categories 1, 2
Aspiration hazard, categories 1, 2

Environment

Hazardous to the aquatic environment, short-term (Acute), category 1
Hazardous to the aquatic environment, short-term (Chronic), categories 1, 2

TABLE 14.3
Hazard (H) Statement Codes for Physical, Health, and Environmental Hazards Specified in the GHS

Physical Hazards
H200—Unstable explosive
H201—Explosive; mass explosion hazard
H202—Explosive; severe projection hazard
H203—Explosive; fire, blast or projection hazard
H204—Fire or projection hazard
H205—May mass explode in fire
H206—Fire, blast or projection hazard; increased risk of explosion if desensitizing agent is reduced
H207—Fire or projection hazard; increased risk of explosion if desensitizing agent is reduced
H208—Fire hazard; increased risk of explosion if desensitizing agent is reduced
H220—Extremely flammable gas
H221—Flammable gas
H222—Extremely flammable aerosol
H223—Flammable aerosol
H224—Extremely flammable liquid and vapor
H225—Highly flammable liquid and vapor
H226—Flammable liquid and vapor
H227—Combustible liquid
H228—Flammable solid
H229—Pressurized container: may burst if heated
H230—May react explosively even in the absence of air
H231—May react explosively even in the absence of air at elevated pressure and/or temperature
H232—May ignite spontaneously if exposed to air
H240—Heating may cause an explosion
H241—Heating may cause a fire or explosion
H242—Heating may cause a fire
H250—Catches fire spontaneously if exposed to air
H251—Self-heating: may catch fire
H252—Self-heating in large quantities; may catch fire
H260—In contact with water releases flammable gases that may ignite spontaneously
H261—In contact with water releases flammable gas
H270—May cause or intensify fire; oxidizer
H271—May cause fire or explosion; strong oxidizer
H272—May intensify fire; oxidizer
H280—Contains gas under pressure; may explode if heated
H281—Contains refrigerated gas; may cause cryogenic burns or injury
H290—May be corrosive to metals
Health Hazards
H300—Fatal if swallowed
H301—Toxic if swallowed
H302—Harmful if swallowed
H303—May be harmful if swallowed
H304—May be fatal if swallowed and enters airways
H305—May be harmful if swallowed and enters airways
H310—Fatal in contact with skin
H311—Toxic in contact with skin
H312—Harmful in contact with skin
H313—May be harmful in contact with skin
H314—Causes severe skin burns and eye damage
H315—Causes skin irritation

(*Continued*)

TABLE 14.3 (*Continued*)
Hazard (H) Statement Codes for Physical, Health, and Environmental Hazards Specified in the GHS

H316—Causes mild skin irritation
H317—May cause an allergic skin reaction
H318—Causes serious eye damage
H319—Causes serious eye irritation
H320—Causes eye irritation
H330—Fatal if inhaled
H331—Toxic if inhaled
H332—Harmful if inhaled
H333—May be harmful if inhaled
H334—May cause allergy or asthma symptoms or breathing difficulties if inhaled
H335—May cause respiratory irritation
H336—May cause drowsiness or dizziness
H340—May cause genetic defects
H341—Suspected of causing genetic defects
H350—May cause cancer
H351—Suspected of causing cancer
H360—May damage fertility or the unborn child
H361—Suspected of damaging fertility or the unborn child
H362—May cause harm to breast-fed children
H370—Causes damage to organs
H371—May cause damage to organs
H372—Causes damage to organs
H373—May cause damage to organs
H300 + H310—Fatal if swallowed or in contact with skin
H300 + H330—Fatal if swallowed or if inhaled
H310 + H330—Fatal in contact with skin or if inhaled
H300 + H310 + H330—Fatal if swallowed, in contact with skin or if inhaled
H301 + H311—Toxic if swallowed or in contact with skin
H301 + H331—Toxic if swallowed or if inhaled
H311 + H331—Toxic in contact with skin or if inhaled
H301 + H311 + H331—Toxic if swallowed, in contact with skin or if inhaled
H302 + H312—Harmful if swallowed or in contact with skin
H302 + H332—Harmful if swallowed or if inhaled
H312 + H332—Harmful in contact with skin or inhaled
H302 + H312 + H332—Harmful if swallowed, in contact with skin or if inhaled
H303 + H313—May be harmful if swallowed or in contact with skin
H303 + H333—May be harmful if swallowed or if inhaled
H313 + H333—May be harmful in contact with skin or if inhaled
H303 + H313 + H333—May be harmful in swallowed, in contact with skin or if inhaled
H315 + H320—Causes skin and eye irritation

Environmental Hazards

H400—Very toxic to aquatic life
H401—Toxic to aquatic life
H402—Harmful to aquatic life
H410—Very toxic to aquatic life with long lasting effects
H411—Toxic to aquatic life with long lasting effects
H412—Harmful to aquatic life with long lasting effects
H413—May cause long lasting harmful effects to aquatic life
H420—Harms public health and the environment by destroying ozone in the upper atmosphere

improper storage or handling of a hazardous product (UNECE, 2015). Similar to hazard statements, precautionary statements are assigned a unique alphanumerical code consisting of the letter P (for precautionary statement), one number designating the type of precautionary statement (1 for general, 2 for prevention, 3 for response, 4 for storage, 5 for disposal), and a two-digit number for sequential numbering of the precautionary statement. A complete list of precautionary statements is provided in Table 14.4

TABLE 14.4
Precautionary (P) Statement Codes Specified in the GHS

P101—If medical advice is needed, have product container or label at hand
P102—Keep out of reach of children
P103—Read label before use
P201—Obtain special instructions before use
P202—Do not handle until all safety precautions have been read and understood
P210—Keep away from heat, hot surfaces, sparks, open flames, and other ignition sources. No smoking
P211—Do not spray on an open flame or other ignition source
P212—Avoid heating under confinement or reduction of the desensitized agent
P220—Keep away from clothing and other combustible materials
P222—Do not allow contact with air
P223—Do not allow contact with water
P230—Keep wetted with …
P231—Handle and store contents under inert gas/…
P232—Protect from moisture
P233—Keep container tightly closed
P234—Keep only in original packaging
P235—Keep cool
P240—Ground and bond container and receiving equipment
P241—Use explosion-proof [electrical/ventilating/lighting/…] equipment
P242—Use non-sparking tools
P243—Take action to prevent static discharges
P244—Keep valves and fittings free from oil and grease
P250—Do not subject to grinding/shock/friction/…
P251—Do not pierce or burn, even after use
P260—Do not breather dust/fume/gas/mist/vapors/spray
P261—Avoid breathing dust/fume/gas/mist/vapors/spray
P262—Do not get in eyes, on skin, or on clothing
P263—Avoid contact during pregnancy and while nursing
P264—Wash … thoroughly after handling
P270—Do not eat, drink or smoke when using this product
P271—Use only outdoors or in a well-ventilated area
P272—Contaminated work clothing should not be allowed out of the workplace
P273—Avoid release to the environment
P280—Wear protective gloves/protective clothing/eye protection/face protection
P282—Wear cold insulating gloves and either face shield or eye protection
P283—Wear fire resistant or flame-retardant clothing
P284—[In case of inadequate ventilation] wear respiratory protection
P231 + 232—Handle and store contents under inert gas/… protect from moisture.
P301—IF SWALLOWED:
P302—IF ON SKIN:
P303—IF ON SKIN (or hair):
P304—IF INHALED:
P305—IF IN EYES:

(*Continued*)

TABLE 14.4 (*Continued*)
Precautionary (P) Statement Codes Specified in the GHS

P306—IN ON CLOTHING
P308—IF exposed or concerned:
P310—Immediately call a POISON CENTER/doctor/…
P311—Call a POISON CENTER/doctor/…
P312—Call a POISON CENTER/doctor/…if you feel unwell
P313—Get medical advice/attention
P314—Get medical advice/attention if you feel unwell
P315—Get immediate medical advice/attention
P320—Specific treatment is urgent (see … on this label)
P321—Specific treatment (see … on this label)
P330—Rinse mouth
P331—Do NOT induce vomiting
P332—If skin irritation occurs:
P333—If skin irritation or rash occurs:
P334—Immerse in cool water [or wrap in wet bandages]
P335—Brush off loose particles from skin
P336—Thaw frosted parts with lukewarm water. Do not rub affected area
P337—If eye irritation persists:
P338—Remove contact lenses, if present and easy to do. Continue rinsing
P340—Remove person to fresh air and keep comfortable for breathing
P342—If experiencing respiratory symptoms:
P351—Rinse cautiously with water for several minutes
P352—Wash with plenty of water
P353—Rinse skin with water [or shower]
P360—Rinse immediately contaminated clothing and skin with plenty of water before removing clothes
P361—Take off immediately all contaminated clothing
P362—Take off contaminated clothing
P363—Wash contaminated clothing before reuse
P364—And wash it before reuse
P370—In case of fire:
P371—In case of major fire and large quantities:
P372—Explosion risk
P373—DO NOT fight fire when fire reaches explosives
P375—Fight fire remotely due to the risk of explosion
P376—Stop leak if safe to do so
P377—Leaking gas fire: Do not extinguish, unless leak can be stopped safely
P378—Use … to extinguish
P380—Evacuate area
P390—Absorb spillage to prevent material-damage
P391—Collect spillage
P301 + P310—IF SWALLOWED: Immediately call a POISON CENTER/doctor/…
P301 + P312—IF SWALLOWED: Call a POISON CENTER/doctor//…if you feel unwell
P302 + P334—IF ON SKIN: Wash with plenty of water/…
P304 + P312—IF INHALED: Call a POISON CENTER/doctor/…if you feel unwell
P306 + P360—IF ON CLOTHING: Rinse immediately contaminated clothing and skin with plenty of water before removing clothes
P308 + P311—IF exposed or concerned: Call a POISON CENTER/doctor/…
P308 + P313—IF exposed or concerned: Get medical advice/attention
P332 + P313—If skin irritation occurs: Get medical advice/attention
P333 + P313—If skin irritation or rash occurs: Get medical advice/attention

(*Continued*)

TABLE 14.4 (*Continued*)
Precautionary (P) Statement Codes Specified in the GHS

P336 + P315—Thaw frosted parts with lukewarm water. Do not rub affected area. Get immediate medical advice/attention
P337 + P313—If eye irritation persists: Get medical advice/attention
P342 + P311—If experiencing respiratory symptoms: Call a POISON CENTER/doctor/…
P361 + P364—Take off immediately all contaminated clothing and wash it before reuse
P362 + P364—Take off contaminated clothing and wash it before reuse
P370 + P376—In case of fire: Stop leak if safe to do so
P370 + P378—In case of fire: Use…to extinguish
P301 + P330 + P331—IF SWALLOWED: Rinse mouth. Do NOT induce vomiting
P302 + P335 + P334—IF ON SKIN: Brush off loose particles from skin. Immerse in cool water [or wrap in wet bandages]
P303 + P361 + P353—IN ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water [or shower]
P305 + P351 + P338—IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
P370 + P380 + P375—In case of fire: Evacuate area. Fight fire remotely due to the risk of explosion
P371 + P380 + P375—In case of major fire and large quantities: Evacuate area. Fight fire remotely due to the risk of explosion
P370 + P372 + P380 + P373—In case of fire: Explosion risk. Evacuation area. DO NOT fight fire when fire reaches explosives
P370 + P380 + P375 [+ P378]—In case of fire: Evacuate area. Fight fire remotely due to the risk of explosion. [Use…..to extinguish]
P401—Store in accordance with…
P402—Store in a dry place
P403—Store in a well-ventilated place
P404—Store in a closed container
P405—Store locked up
P406—Store in a corrosion resistant/…container with a resistant inner liner
P407—maintain air gap between stacks or pallets
P410—Protect from sunlight
P411—Store at temperatures not exceeding …°C/…°F
P412—Do not expose to temperatures exceeding 50°C/122°F
P413—Store bulk masses greater than …kg/…lbs at temperatures not exceeding…°C/…°F
P420—Store separately
P402 + P404—Store in a dry place. Store in a closed container
P403 + P233—Store in a well-ventilated place. Keep container tightly closed
P403 + P235—Store in a well-ventilated place. Keep cool
P410 + P403—Protect from sunlight. Store in a well-ventilated place
P410 + P412—Protect from sunlight. Do not expose to temperatures exceeding 50°C/122°F
P501—Dispose of contents/container to …
P502—Refer to manufacturer or supplier for information on recovery or recycling

Composition/Information on Ingredients

Section 3 of the SDS describes the chemical identity of the substance, chemical name, synonyms, CAS number, and other identifier for the substance. In addition, this section lists any impurities and/or stabilizing additives, which are classified and contribute to the classification of the substance. For mixtures, it lists the chemical identities, identification numbers, and concentration or concentration ranges of all hazardous ingredients. In some instances, such as an investigational drug, chemicals may be withheld from the SDS due to trade secrets, but this requires a statement that identifies the chemical being withheld and the exact percent (concentration) of the compound(s).

First-Aid Measures

Section 4 describes the initial care that can be given by an untrained responder to an individual who has been exposed to the chemical or mixture. Information listed in this section includes necessary first-aid instructions by the relevant routes of exposure including inhalation, skin and eye contact, and ingestion. The section describes the most important symptoms or effects, both immediate and delayed, and advises whether movement of the exposed individual, removal of clothing and shoes, or use of personal protective equipment (PPE) is recommended or not. Where appropriate, the section also lists information on clinical testing and medical monitoring for delayed effects, antidotes, and contraindications.

Fire-Fighting Measures

Section 5 of the SDS provides recommendations for fighting a fire caused by the substance or mixture, or a fire arising in its vicinity. This section lists information on the appropriate extinguishing media and indicates any extinguishing media, which are inappropriate for the substance or mixture. Specific hazards that may arise from the chemical, including hazardous combustion products that form when the substance or mixture burns, are also listed as are recommendations on special equipment or precautions for firefighters.

Accidental Release Measures

Section 6 provides recommendations on the appropriate response to spills, leaks, or releases, along with containment and cleanup practices to prevent or minimize exposure to people, properties, or the environment. It may also include recommendations distinguishing between responses for small and large spills where the spill volume has a significant impact on the hazard. The required information may consist of recommendations for use of personal precautions, emergency procedures, and protective equipment for non-emergency and emergency personnel. Advice for any environmental precautions related to accidental spills and release of the substance or mixture are included in this section. It also provides methods and materials for containment and cleaning up.

Handling and Storage

Section 7 of the SDS provides guidance on the safe handling practices and conditions for the safe storage of chemicals that minimize the potential hazards to people, property, and the environment from the substance or mixture. Typically, advice on general hygiene is included in this section, such as, “eating, drinking, and smoking during use is prohibited,” “wash hands after use,” and “remove contaminated clothing and protective equipment before entering eating areas.” Advice on specific storage requirements, such as ventilation and temperature requirements, are included.

Exposure Controls/Personal Protection

Section 8 indicates the exposure limits, engineering controls, and personal protective measures that can be used to minimize worker exposure. Any occupational exposure limit values are listed for the substance or mixture. These include OSHA Permissible Exposure Limits (PELs), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), and any other exposure limit used or recommended by the chemical manufacturer, importer, or employer preparing the safety data sheet, where available. Examples of appropriate engineering controls include “use local exhaust ventilation” or “use only in an enclosed system.” This section identifies the PPE (such as eye/face, skin, and respiratory protection, and garments to protect against thermal hazards) needed to minimize the potential for illness or injury due to exposure to the substance or mixture.

Physical and Chemical Properties

Section 9 of the SDS identifies physical and chemical properties associated with the substance or mixture. At a minimum, the SDS lists information on the following:

- Physical state
- Color
- Odor
- Melting point/freezing point
- Boiling point or boiling point range
- Flammability
- Lower and upper explosion limit/flammability limit
- Flash point
- Auto-ignition temperature
- Decomposition temperature
- pH
- Kinematic viscosity
- Solubility
- Partition coefficient n-octanol/water (log value)
- Vapor pressure
- Density and/or relative density
- Relative vapor density
- Particle characteristics

For those sections where information is not available, they should still be listed in the SDS with the statement *not available*.

Stability and Reactivity

Section 10 of the SDS describes the reactivity hazards and stability information for the chemical or mixture. The section provides specific test data, where available, for the substance or mixture, as a whole. However, the information may also be based on general data for the class or chemical family. In addition to chemical stability and reactivity, this section lists conditions to avoid (such as heat, pressure, shock, static discharge, vibrations, or other physical stresses that might result in a hazardous situation), incompatible materials, and any known or reasonably anticipated hazardous decomposition products.

Toxicological Information

Section 11 identifies the toxicological and health effects information or indicates that such data are not available. At a minimum, the relevant hazards, for which data should be provided are:

- Acute toxicity
- Skin corrosion/irritation
- Serious eye damage/irritation
- Respiratory or skin sensitization
- Germ cell mutagenicity
- Carcinogenicity
- Reproductive toxicity
- Specific Target Organ Toxicity (STOT)—single exposure
- STOT—repeated exposure
- Aspiration hazard

The health effects included in this section of the SDS should be consistent with those described in the studies used for the classification of the substance or mixture. Depending on the amount of data available, it may be summarized by route of exposure. If data for these hazards are not available, they should still be listed on the SDS with a statement that data are not available. In addition, any negative data should also be provided.

Ecological Information

Section 12 of the SDS provides information to evaluate the environmental impact of the chemical or mixture if it were released to the environment. Data from toxicity tests performed on aquatic and/or terrestrial organisms, where available (e.g., acute or chronic aquatic toxicity data for fish, algae, crustaceans, and other plants; toxicity data on birds, bees, plants) are included in this section. Information on the chemical or mixture's potential to persist and degrade in the environment either through biodegradation or other processes, such as oxidation or hydrolysis Information on potential bioaccumulation or groundwater contamination is listed in this section. Other adverse effects listed in Section 12 include environmental fate, ozone layer depletion potential, photochemical ozone creation potential, endocrine disrupting potential, and/or global warming potential.

Disposal Considerations

Section 13 of the SDS provides information for proper disposal, recycling or reclamation of the substance or mixture and/or its container to assist in the determination of safe and environmentally preferred waste management options, consistent with the requirements of the national competent authority. Specifically, the section should specify disposal containers and methods, discuss physical/chemical properties that may affect disposal options, discourage sewage disposal, and identify any special precautions for incineration or landfill.

Transport Information

Section 14 provides basic classification information for the transporting and/or shipping of a hazardous substance or mixture by road, rail, sea, or air. When information is not available or relevant, it should be stated in this section. Information listed in this section includes:

- UN number (four-figure identification number of the substance or article) from the UN Model Regulations
- UN proper shipping name from the UN Model Regulations
- Transport hazard class
- Packing group
- Environmental hazards
- Special precautions for user
- Guidance Transport in bulk

Regulatory Information

Section 15 of the SDS provides any safety, health, and environmental regulations specific for the product that is not indicated anywhere else within. The information may include any national and/or regional regulatory information of the chemical or mixtures (including any OSHA, Department of Transportation, Environmental Protection Agency, or Consumer Product Safety Commission regulations).

Other Information

Section 16 provides information relevant to the preparation of the SDS, including:

- The date of preparation of the latest revision of the SDS
- A key/legend to abbreviations and acronyms used in the SDS
- Key literature references and sources (not required)

INTERNATIONAL ASPECTS

Based on the differences of hazard definitions and percentage thresholds for hazardous components of mixtures, SDS writing teams, who work for multinational companies, certainly have a challenge in providing MSDSs that meet all national requirements while achieving a level of consistency in warnings to all customers. Legal consultation is advisable before establishing compliance programs. All options are problematic. A worst-case SDS using the most conservative hazard definition may cause customer perception problems. Separate SDSs for each jurisdiction using each local requirement would cause problems with multinational customers who would receive different SDSs on the same product. This may also cause product liability problems in the US.

The need for a GHS was endorsed by the 1992 UNCED. The GHS, first published in 2003 and currently in its sixth revised edition, establishes harmonized hazard classification and communication provisions with explanatory information on how to apply the system. However, the GHS itself is not a regulation or standard. The GHS SDS format has been widely accepted by the United States, Europe (European Union), Canada, Australia, Brazil, China, and Japan. However, some countries have not adopted or only adopted parts of the GHS. Others are in different transitional periods for substances and mixtures. As a result, differences in SDS formats and/or requirements are seen from country to country.

LABELING FOR TRANSPORTATION

Transportation specialists, in conjunction with toxicologists, hazard communication specialists, and chemical regulatory specialists, are responsible for complying with classifying, labeling, marking, placarding, and manifesting requirements. Information required on a GHS label includes appropriate signal words, hazard statements, precautionary statements, pictograms, product identifiers, and supplier identification, as listed on the SDS (UNECE, 2015). It is important to note that in the US, the pictograms established by GHS and adopted by OSHA, do not replace the diamond-shaped labels that the US Department of Transportation (DOT) requires for transportation of chemicals.

Most companies use integrated computer and printing systems to generate a single product label that meets OSHA Hazard Communication Standard (HCS) and DOT Hazardous Material Transport Act (HTMA) requirements. Regulations of other organizations that need to be considered include: ICAO/IATA (international air transport) (ICAO, 1999; IATA, 1999), IMDG (international sea transport) (IMO, 1998), ADR/RID (European land transport) (Economic Commission for Europe, 1998), TDG (Canadian land transport) (Transport Canada, 1998), ADG (Australian land transport) (Australian Code for the Transport of Dangerous Goods by Road and Rail, 1998) and Official Mexican Standards, called Normas or NOMS (Mexican non-bulk land transport) (Official Mexican Standards, 1995). Programs exist in the US (CHEMTREC) and Canada (CANUTEC) to assist emergency responders in dealing with accidents occurring during the transportation of chemical shipments.

CONCLUSIONS AND FUTURE CONSIDERATIONS

Hazard communication regulations have been profoundly successful in that they have fundamentally changed the way industry operationally deals with chemicals. Work forces are trained to read SDSs before working with a new chemical. Workplace and transport labels with hazard symbols offer immediate recognition of the acute health hazards to workers, carriers, customers, and the general public. In many corners of the world, all this was accomplished via a variety of performance standards that allow flexibility in addressing complex physical and health hazard information. Even though SDSs and labels are not required all over the world, almost all chemical products are labeled and accompanied by an SDS no matter what the destination might be due to systems in place with manufacturers to satisfy the requirements of customers in the regulated countries.

Given the current state of extensive global trade in chemicals, the need to develop an internationally harmonized system to ensure their safe use, transport, and disposal was recognized as vital. Following more than a decade of work, the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) was developed and has been adopted my many countries around the world, thus increasing consistency in classification systems and hazard communication. This is not to say that further improvements in hazard communication regulations and compliance programs are not desirable. It is hoped that continued improvement contributes in no small way to a reduction in occupational injuries and illnesses.

Websites of Interest

Government Agencies	
Department of Justice (Canada)	www.canada.justice.gc.ca
PHMSA (Pipeline and Hazardous Materials Safety Administration)	http://www.phmsa.dot.gov/hazmat
ECE Transport (EU)	www.unece.org/trans
EPA (US)	www.epa.gov
Health Canada	www.hc-sc.gc.ca
Government Publishing Office (US)	www.gpo.gov
Japan (METI)	www.meti.go.jp
OSHA (US)	www.osha.gov
Transport Canada	www.tc.gc.ca
Safe Work Australia	www.safeworkaustralia.gov.au
Organizations and Expert Bodies	
ACGIH	www.acgih.org
CANUTEC	www.tc.gc.ca/canutec
CHEMTREC	www.cmahq.com
IARC	www.iarc.org.fr
IATA	www.iata.org
IMO	www.imo.org
NTP	www.ntp-server.niehs.gov
OECD	www.oecd.org
UNECE	http://www.unece.org/info/ece-homepage.html

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15 Genetically Modified Organisms—Evolution or Revolution of Genetics

Assessing the Health Risks of Foods and Crops

John A. Budny

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Clarity is important for understanding issues or concepts, especially those with technical components. The importance of clarity increases when an issue or concept requires choices and decisions that society makes for itself. In the minds of the individual members of society, the importance of any issue is magnified if the issue is personal and intimate such as choices for food consumption. For these reasons, toxicologists must unambiguously assess the risks of genetically modified foods intended to be consumed directly or genetically modified crops fed to animals, which then are consumed for food. While there are many sources for the lack of clarity on the issues related to genetic modification of foods and crops, the toxicologist must not be one of them.

The foundation of clarity is definitional precision. Consequently, it is important to explain what terms mean and how they will be used in discussing organisms, ingested foods and crops that have been genetically altered. A genetically modified organism (GMO) can be either an organism (in its broadest sense by being unicellular or multicellular), an agricultural commodity, an ingested food, or an ingested food component, including processed food. Genetic

modification (GM) is one of two broad processes by which an organism can be genetically altered or genetically changed. GM can be a descriptor for an object that has had its genetic material changed or an action such as carrying out genetic alterations. One process to affect the genetic change is breeding or mating. The other way to bring about a change in an organism's genetic material occurs when the organism's genetic composition is changed at the molecular level using biochemical techniques. GE, like GM, can be a descriptor for an organism that had been genetically engineered or an action such as carrying out genetic engineering. GMO is the term that is widely used by society to describe GM or GE organisms and products. Since society prefers using the term GMO, it is important for the toxicologist to understand that society will rarely make the distinction between organisms or products that are GM by mating or breeding techniques and those organisms or products whose genetic constitution is altered through GE. In short and in a practical sense for the toxicologist, GMO, GM, and GE is a blur in the consumer's mind.

In addition to the lack of clarity in the consumer's mind among GMO, GM and GE, most members of society will give only a polite nod to any distinctions between the food that they eat and a raw agricultural commodity (crop). Furthermore, the consumer will likely be unaware of the inherent complexities and difficulties in detecting genetic differences between outwardly similar crops or the consumable foods made from them.

In this discussion, GMO is used to describe both crops and processed food derived from the crops. In addition, GM and GE may be used interchangeably, realizing that breeding and mating is different from engineering at the molecular level. However, the end result from each process may be similar or identical. It is the role of the toxicologist to determine if there are potential health risks of subtle and often imperceptible differences between a genetic change, which occurred through breeding or mating, and one that occurred through GE.

HUMAN EVOLUTION AND ITS IMPACT ON GENETICALLY MODIFIED ORGANISMS

As humans evolved, there was a transformation of the society in which they lived. Human activity for survival changed from hunter-gatherer functions into activities more aligned with societies that can be best described as non-migratory agronomic enclaves. Once a society gave up its nomadic ways, there was a shift from taking and using available agricultural output, as it existed, to modifying the nascent food and fiber to meet the specific needs of a stationary society. The phenotypic modulation of the society's food source was done on a gross scale using sexual or breeding techniques resulting in domestication of plants and animals to meet the then current and ever-developing needs of the society.

Domestication through heuristic breeding was the driver of phenotypic expression until the door to selective and designed genotypic modulation was opened by the Austrian monk Gregor Mendel in the mid-1800s. It wasn't until the early 1900s when there was a full appreciation of Mendel's insight that the genotypic constitution of an organism regulates its phenotypic expression. During those times, progress in the development of genetics was determined by the calendar—seasons, life cycles, gestation periods, and so on. Without molecular biochemical tools, breeding was the only experimental avenue available to definitively connect genotypic constitution to phenotypic expression. Suddenly a discovery, akin to that of Mendel, was made in the mid-1970s when Herbert Boyer and Stanley Cohen introduced the opportunity to change phenotypic expression from a breeding-driven activity to manipulating an organism's genetic composition by direct intervention at the molecular level. The intent and objective of controlling traits and characteristics of plants and animals remained the same, but the way the objective was achieved for over 10,000 years took a dramatic turn.

Today genome editing is fast, efficient, and precise. Sophisticated genome editing at the molecular level using nucleases began in the mid-1990s with zinc finger nucleases (ZNFs), which was followed by transcription activator-like effector nucleases (TALENs). These two genomic editing

tools have largely been replaced by a RNA-guided endonuclease systems (RGENs). The one that is currently used is the clustered regularly interspaced short palindromic repeat (CRISPR)-associated system and specifically the CRISPR/Cas9 system. The RGEN system of CRISPR/Cas9 provides substantial improvement over ZFNs and TALENs. The most notable improvement is that the CRISPR/Cas9 gene editing system has a reduced potential of health risks, by decreasing off-target modifications and by not leaving any residual genetic material that is extraneous to the modified organism (Bortesi 2015; Woo, et al. 2015; Osakabe 2015; Kumar 2015; Kleinstiver 2016).

The ever-present laws of nature, such as the fundamental directives for thermodynamics, kinetics, mass action, conservation of mass, homeostasis, and so on, govern the genetic constitution of plants and animals, not the method by which the genetic constitution or composition is achieved. These laws do not distinguish between errors in nature or those errors that are toxicological misadventures resulting from GE. It makes no difference if the plants and animals have new phenotypic traits which were the result of breeding and sexual activity or whether the new traits were the result of asexual, molecular manipulation. The focus, for any real or theoretical human health risk associated with GE food or crop, is on the product or result (food or crop) and not on the process by which the product was produced.

EVALUATION OF SOCIETAL RISKS

In 2010, GE crops were grown on over 309 million acres in 25 countries with more than half of this acreage in the US followed by Argentina, Brazil, Canada, and China. In the total acreage of GE crops, the two most prominent traits that were expressed were herbicide tolerance and insect resistance. However, as the use of the technology expands, other traits, such as virus resistance, increase in crop quality and productivity, drought resistance, and so on, will be gaining interest. When multiple traits, such as herbicide tolerance and insect resistance, are incorporated into a single GE plant, the process is called *stacking*, and the result is a *stacked* crop (Que, et al. 2010; Agapito-Tenfen, et al. 2014). Stacking adds an additional level of complexity to the risk assessment process for GE.

Society in making decisions about xenobiotics uses the benefit/risk framework, which by its nature is a binary process; the good or benefit of the xenobiotic is weighed in light of the risks that it presents. The toxicologist's prevue, while addressing the risk by defining the hazard and when necessary and appropriate to do so, the likelihood that the hazard will manifest itself, will have an interest, if only in a passive way, in the benefit component of the framework. In the case of GE food and fiber and the GMOs that are used and consumed by humans and animals, there are numerous opportunities for beneficial outcomes. The economic and social benefits, as well as GE's contribution to food security for an ever-expanding world population have been identified and discussed (Qaim 2016a; Brooks and Barefoot 2014; Christou et al. 2006; Ferry et al. 2006; Krockaert et al. 2015; Cohen and Paarlberg 2004; Qaim and Zilberman 2003; Huang et al. 2005; Ramessar et al. 2007; and Toenniessen et al. 2003).

REGULATING GENETICALLY MODIFIED FOODS

The regulatory approaches for GE raw agricultural commodities and finished food products throughout the world are diverse (Ledford 2016). Political, economic, and cultural influences determine how regulatory frameworks are constructed by a wide variety of governmental organizations. The regulatory agencies claim, in various degrees, mandatory and voluntary influence and control over petitioners who file applications for various GE entities in the food production chain (NAS Committee 2016; European Commission 2013). There are also guidance, advice, and suggestions layered upon the regulatory mandates by various organizations, such as World Trade Organization (World Trade Organization 2016), Codex Alimentarius Commission Codex Alimentarius Commission 2009), European Food Safety Authority (ESFA 2004), and so on. There are also various country-specific regulatory organizations.

Individual governments, through their respective regulatory agencies, have crafted regulations that have various degrees of discord among them. In some cases, the process for making the GE product is regulated and in other cases, the product and not the process by which it is made is regulated. The attitude of the specific country also plays a part in how rigorous a country's regulation will be defined. Countries have been segregated into four policy option toward GE products, for example, Promotional, Permissive, Precautionary, or Preventive (Paarlberg, 2000). The selected policy option for a country is defined by its society. Karlberg was able to segment each of the policy options into specific attitudes such as intellectual property rights, biosafety, trade, food safety, consumer choice and public research investment. Some countries' regulatory bodies address only biosafety issues while other countries go beyond safety issues. The breadth of regulatory expansion is extensive, including a reach into socioeconomic concerns such as Right-to-Know (Hemphill, et al., 2015; Armenakas and Alexiades-Armenakas, 2013) and non-food impacts on farmers who cultivate GE crops (Racovita, et al. 2015). Finally, not all regulatory schemes are consistent in how they arrive at decisions on GE crops by political bodies that may or may not use qualified expert opinions. Regulatory decisions, which go beyond human and animal health risks, open the door to a hot mess of ill-informed decisions from political groups with ideological agendas.

The socio-political difference between the US and the EU is reflected in the perceived and implemented policy options between the two societies. While regulations in the US tend to promote GE food and crops, there is a precautionary flavor to the EU structure and regulations. These differing approaches confuse rather than clarify issues for the consumer. If, in the consumer's mind the confusion results in fear, then it wouldn't be surprising for the consumer to take a precautionary approach.

WHAT DRIVES ATTITUDE AND REGULATIONS OF GENETICALLY ENGINEERED FOODS AND CROPS?

The rate at which countries incorporate GE food and crops into their agricultural programs is dependent upon the country's attitude toward biotechnology and in the case of agriculture, GE foods and crops. Many dimensions, such as safety of the GE crop for humans, livestock, and the environment, affect the attitude toward GE food and crops. In addition, consumer acceptance of GE foods affects trade interactions among countries.

Paarlberg identified the type and range of choices and what influences them (Paarlberg 2000). His analysis is summarized in Table 15.1. The attitude of a society or country in shaping a society's predisposition to a particular policy toward GE foods and crops range from very supportive of and *Promotional* to less enthusiastic but, nonetheless, *Permissive* toward the technology by allowing GE foods and crops into their agricultural commerce but not facilitating GE activities to infiltrate their agricultural programs. Other societies or countries invoke a *Precautionary* stance toward GE foods and crops, being cautious of any risks that may be known and fearful of potential risks that are unknown. Without having a program for re-evaluation, or if having a re-evaluation program yet failing to use it for precautionary-based decisions, the precautionary approach can easily become a *de facto* rejection by either intentionally or unintentionally failing to update decisions (Hansson, 2016). The *Preventive* policy of a society toward GE foods and crops is self-explanatory. While the issue of a *Preventive* policy is intellectually interesting, providing a wide range of social, political, and ethical considerations some of which are related to motives behind the policy, the *Preventive* policy has little interest for a toxicologist since a risk assessment is precluded. Cohen and Paarlberg have published an interesting and informative discussion concerning the implementation of GE food and crops in developing countries. Even though GE crops can provide valuable contributions to sustainable agriculture, disputes continue and permissions to plant GE crops have not been granted in most developing countries (Cohen and Paarlberg, 2004).

TABLE 15.1
Policy Options Toward GM Crops

	Promotional	Permissive	Precautionary	Preventive
Intellectual property rights	Full patent protection, plus plant breeder' rights under UPOV 1991	PBRs under UPOV 1991	PBRs under UPOV 1978, which preserves farmer' privilege	No IPRs for plants or animals, or IPRs on paper that are not enforced
Biosafety	No careful screening, only token screening or approval based on approvals in other countries	Case-by-case screening for demonstrated risk, depending on intended use of product	Case-by-case screening also for scientific uncertainties owing to novelty of GM process	No careful case-by-case screening; risk assumed because of GM process
Trade	GM crops promoted to lower commodity production costs and boost exports; no restriction on imports of GM seeds or plant materials	GM crops neither promoted nor prevented; imports of GM commodities limited in same way as non-GM in accordance with science-based WTO standards	Import of GM seeds and materials screened or restrained separately and more tightly than non-GM labeling requirements imposed on import of gm foods or commodities	GM seed and plant imports blocked; GM-free status maintained in hopes of capturing export market premiums
Food safety and consumer choice	No regulatory distinction drawn between GM and non-GM foods when testing or labeling for food safety	Distinction made between GM and non-GM foods on some existing food labels but not to require segregation of market channels	Comprehensive positive labeling of all GM foods required and enforced with segregated market channels	GM food sales banned or warning labels that stigmatize GM foods as unsafe to consumers required
Public research investment	Treasury resources spent on both development and local adaptations of GM crop technologies	Treasury resources spent on local adaptations of GM crop technologies but not on development of new transgenes	No significant treasury resources spent on GM crop research or adaption; donors allowed to finance local adaptions of GM crops	Neither treasury nor donor funds spent on any adaptation or development of GM crop technology

Source: Paarlberg, *Governing the GM Crop Revolution*: *Policy Choices for Developing Countries*. Food, Agriculture, and the Environment Discussion Paper 33. Table. International Food Policy Research Institute, Washington, DC, 2000.

Note: UPOV = Union for the Protection of New Varieties of Planet; PBRs = plant breeders' rights; WTO = World Trade Organization.

REGULATION OF GENETICALLY ENGINEERED FOODS AND CROPS IN THE UNITED STATES

Until 2016, the US did not have any federal laws and subsequent federal regulations specifically aimed at GE food and crops. Instead, GE food and crops were regulated under the Coordinated Framework for the Regulation of Biotechnology (Coordinated Framework), which focuses on the products rather than the process by which the products are made (NAS Committee, 2016; Library of Congress, The Law Library of Congress, Global Research Center, 2014; Yang and Chen, et al. 2016; Belson, 2000). In 2016, The Agricultural Marketing Act of 1946 was amended with the addition of "Subtitle E—National Bioengineered Food Disclosure Standard," which is more commonly known as a GMO labeling bill (Anonymous, 2016). The GMO labeling bill is essentially a right-to-know directive, which is part of

agricultural legislation that will be implemented and enforced by the labeling activities that are currently carried out under the Federal Food Drug and Cosmetic Act (21 USC. 301 et seq.), Federal Meat Inspection Act (21 USC. 601 et seq.), Poultry Products Inspection Act (21 USC. 451 et seq.), or the Egg Products Inspection Act (21 USC. 1031 et seq.). The GMO Labeling Bill with its right-to-know consideration for consumers, will be implemented and administered by the US Food and Drug Administration even though it was attached to the Agricultural Marketing Act of 1946.

The Coordinated Framework is a confederation of three regulatory agencies: US Department of Agriculture (USDA), US Environmental Protection Agency (EPA), and the Federal Food and Drug Administration (FDA). Published in the Federal Register on June 26, 1986, the Coordinated Framework for regulating GE plant-derived food and fiber products laid out the direction that there would not be a whole new industry created by new biotechnology regulations. Rather, the regulation of biotechnology would be addressed within the framework of existing regulations with their defined scope (breadth and depth) and jurisdictional designations. The creation of the Coordinated Framework resulted in two benefits: (1) avoided unnecessary and burdensome regulatory growth with its additional costs and confusion and (2) put the regulatory focus for biotechnology on products rather than the process by which GE products were made. The Coordinated Framework resulted in regulatory management that was decentralized without creating an additional layer of bureaucracy.

The concept of regulating the GE product rather than the process or the technology is reinforced by giving the regulatory attention to points of risk in the product or material flows. Within the USDA, the Animal and Plant Health Inspection Service (APHIS), which is responsible for protecting agricultural commodities (crops that have been grown and entered into commerce) from pests and diseases, has responsibility for GE plants and considers them as regulated articles. Additional clarification issued by USDA (USDA 2018) reinforced the Agency's oversight of plant material produced using GE. The Agency listed hybridization and mutagenesis using chemical or radiation techniques as methods equivalent to common plant breeding processes in their outcomes. The processes that result in DNA deletions of all sizes, single base-pair substitutions and DNA insertions from related plants will be viewed by the Agency as equivalent to normal and historical techniques. The Agency will continue to regulate and presumably conduct human risk assessments of GE plants in which non-plant genes are introduced into plant material. The clearly stated regulatory focus of the USDA is on protecting plant health.

The EPA, through the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and its definition of *pesticide*, has regulatory jurisdiction of plants growing in the field. The EPA regulates attempts to reduce or eliminate pest or disease stressors to plants through genetic manipulation or GE. As an example, seeds for crops are developed through GE to become herbicide tolerant so that weed control can be carried out on the crop as it is growing without causing injury to the crop plants, are regulated by the EPA. In addition, EPA also sets residue limits for xenobiotics for foods that are consumed. Finally, a GE crop may, at times, be considered a new chemical entity that may not fall under the classification of a drug, pesticide, or a substance, which is not regulated by any laws other than the Toxic Substances Control Act (TSCA). The EPA also administers the TSCA regulations and its requirements.

The FDA serves as the focal point for the integrity and safety of the food supply for the United States. Having the historic responsibility for the US food supply, the experience of GE drugs and biologics and the labeling jurisdiction for foods, makes the FDA the regulatory agency of choice for GE food interface with the consumer. Consistent with the regulatory theme outlined for USDA and EPA, the FDA regulates GE products and not the process that is used in making the GE product. The regulatory balance was exquisitely delineated by the USDA (USDA 2018) by defining the regulatory scope of the USDA, FDA and EPA: USDA's regulatory scope covers protecting plant health; FDA assures food and feed Safety; and EPA regulates the sale, distribution and testing of GM raw agricultural commodities for the protection of environmental health and conditions that present risks to humans from the environment. While it is a delicate balance among the three regulatory agencies, it is clear that they have a unified focus on product and not process regulation.

The rational approach of the US regulatory scheme under the Coordinate Framework for the Regulation of Biotechnology Products sets the stage for, what has turned out to be, consumer sense and defensible regulation of GE food. Evaluating the GE products, rather than bringing under scrutiny the process by which they are made, emphasizes the absurdity of emotional reactions toward GE foods and the ideologically laden terms such as *Franken Food* and *Killer Crops*.

REGULATION OF GENETICALLY ENGINEERED FOODS AND CROPS IN THE EUROPEAN UNION

The regulations in the EU for GE foods and crops are found in two regulatory documents from the European Commission and published in the Official Journal of the European Union (European Commission 2003, 2013). All of the documents outlining the various regulations can be found on the EU law website entitled Access to European Union Law (EUR-Lex 2016). In addition, the European Food Safety Authority website has extensive resources, including regulations and guidance documents for those professionals making health risk assessments for GE foods and crops (European Food Safety Authority 2016).

The focus of GE regulations for food and crops in the EU, unlike the US, is on how the GE food or crop seed is made. In the US, the decision to regulate GE food or crops is not how the food or crops are produced but rather the existing regulations for any food or crops, whether or not they are GE. In the EU the definition and description of regulated food or crops, mating and breeding are considered *natural* while molecular manipulations of genetic materials are considered *unnatural* and are required to go through the regulatory process. This is a harsh and polarizing view of GE processes and biotechnology in general, leading to ideological assaults on genetic engineering

The philosophical directive, which establishes the level of risk for GE food and crops in the EU, is based on the Precautionary Principle (Paarlberg, 2002; Weimer, 2010; von Schomberg, 2012; Hansson, 2016). Precautionary Principle for risk management has some problems that undermine not only the advance of biotechnology as a science, but also inhibits technological progress that is necessary to meet the increasing world demand for food (Hansson, 2016; Qaim, 2016a).

Given that there is a diversity in the policy approaches laid out in Table 15.1 for regulation of GE food and crops, the variability does not stop at policy. In a similar manner, there is a divergence in the focus of regulations. In the US, GE food and crop regulations are aimed at specific products that embody GE technologies. In the EU, the GE regulations are directed at the specific technology that creates the GE product and not the product itself. Lynch and Vogel maintain that the difference in the way the US and the EU regulate GE food and crops is due to the divergence in the way the two societies view and regulate risk (Lynch and Vogel 2001).

Yet with the stark contrast and difference between the US and the EU, there are some who believe that the safety assessment for GE crops *are harmonized world-wide to a large extent* and any differences in regulations between the EU and the rest of the world are limited to the regulation of stacked GE crops (Kok, et al. 2014). Such a parochial view does not comport with reality when more than half of the GE crops that are grown in the world are grown in the US (Que, et al. 2010), which has a dramatically different policy approach for regulating GE crops (Table 15.1).

In the US, the concept of *substantial equivalence* has been used and is the framework for identifying any hazards or toxicities resulting from products that are produced through GE technology (NAS 2016). Substantial equivalence is a reasonable and cost-effective approach to assess any toxicities that may emerge from toxins, nutrient changes, newly introduced foreign genes, changes in nascent metabolites associated intermediary metabolism, or the introduction of new or modified proteins. However, *substantial equivalence* is not an assessment in and of itself. Rather, it is a guidance factor when designing a toxicology testing program for GE products.

The *substantial equivalence* paradigm goes beyond toxicology. When used to guide an analytical testing program, the *substantial equivalence* analytical assessment can give insight to the toxicologist for identifying changes in the nutritional components and metabolites or the appearance of new or different genetic material and foreign proteins.

AND THEN THERE IS TOXICOLOGY...

Putting aside the GE foods and crops regulatory dimension, laden with maximum-tolerated-doses of sociology, psychology, political ideologies, public relations, and bureaucracy, there are important toxicology issues that beg for attention. These toxicology issues and questions cannot be addressed competently using a populist approach, and science is not a democratic endeavor where voting makes it so. Standard testing protocols and guidelines, such as those from OECD (OECD Guidelines for Testing of Chemicals. Section 4. Health Effects 2016), do not work well for defining toxicities and hazards for materials that are derived from GE processes. The process for making GE food and crops is still on the upside of the development curve with a wide-open throttle that rivals Moore's Law (Investopedia 2016). The time is right for wisdom, clear thinking, and good science which will result in an ample dose of clarity.

Toxicologists are called upon to assess the hazards (toxicities) of xenobiotics, which are either stand-alone toxicants or are part of a composition—natural or man-made. This established and routine procedure takes a sharp turn for assessing the toxicities of GE foods and crops. In the case of assessing a GE food or crop, a gene, which is a normal constituent of a plant, is transformed by editing the plant's genes, changing or altering it into a xenobiotic—a unique and unfamiliar scenario for a toxicologist. The bizarre nature of the scenario, a new gene that is a xenobiotic, is not yet finished. The newly created xenobiotic, a modified gene, has, in many cases, the ability to generate a second xenobiotic, which is usually a protein such as an insecticidal protein. While this process is the intended one, it is not one that lends itself to standard or routine toxicology testing. The scenario does argue for a case-by-case approach because it is a unique circumstance to purposefully change an organism's proteome.

Settling the quasi-philosophical issue is beyond the scope of this discussion. However, bringing up the issue of standardized toxicity testing raises the question about the validity of the hazard assessments that were conducted for GE food and crops in the past and continue to be conducted with faulty science (Goodman 2011). One example of the uniformity in the EU is the mandated requirement that animal studies used for evaluating toxicity be done with *whole foods* (WF) fed from a GM crop and compared to the same crop that is not GE (European Commission 2013; Bartholomeus, 2013). While WF studies are required in the EU, they are not required elsewhere, including the US. Many investigators using the *whole food* approach for dosing in standardized toxicity tests, such as the 90-day feeding study, failed to show any adverse effects (MacKenzie, et al. 2007; He, et al. 2008, 2009; Liu, 2012). Intuitively, conducting toxicity studies using WF seems on the surface to be a reasonable approach, however, the evidence of published studies hints otherwise (Schmidt, et al. 2016; Bartholomaeus, et al. 2013).

It is not surprising that many of the subchronic toxicology studies using WF as the test article showed only minimal effects which were hardly adverse and easily could have been considered normal animal variability. The GE plants expressed the intended protein at very low levels resulting in <0.2% of the total protein in the plant (Goodman, 2011; Betz, 2000). It was impossible to achieve a level of the expressed protein using a WF test article to induce any kind of toxicity. In effect, and based on the EU regulatory requirements, the 90-day feeding studies were not toxicity studies aimed at defining toxicity; rather they were flawed attempts to demonstrate safety. Any toxicity study without a clear-cut toxicity and the doses at which it the effect does and does not occur, has dubious value.

In one of its many projects, the European commission funded a project entitled *New Methods for the Safety Testing of Transgenic Foods*, which was called SAFOTEST. Knudson et al. improved the *substantial equivalence* approach for toxicity testing in feeding studies by modifying the standard 90-day feeding study using WF with the addition of a 28-day study, testing the purified GE product and spiking with the purified gene product. Comparisons can be made between a non-transgenic WF and a transgenic WF using information obtained with the combination of the transgenic WF plus the spiking of the GE product (Knudsen and Poulsen 2007). With the known product of modified gene in the GE crop, for example, an insecticidal protein, the standard toxicity testing paradigm requires some modification to be applicable to assessing the toxicity of gene in the GE food and crops as well as the gene product of the GE gene. Rather than using a spiking procedure, why not carry out toxicity testing on the known product from the modified gene?

The active discussions of using WF as test articles may have contributed, at least in part, to the work reported by Seralini et al. (Serelini et al. 2012). The reason Serelini et al. gave in their paper for conducting their investigations, however, was that the previously conducted studies were too short. For whatever stated or implied reasons for the Seralini et al. work, the publication of it was withdrawn (Retraction Notice 2014). The work was republished (Seralini et al. 2014) without substantial changes. In this controversial chronic feeding study, the authors described a wide range of toxicities which they claimed were undetected because the previous studies were not of sufficient duration. The Seralini et al. study, along with several of the other studies of shorter duration which were in conflict with the Seralini et al. work were analyzed and reviewed (Jendrysik 2013; Casassus 2014; Genetic Literacy Project 2012).

Several investigators have identified the specific difficulties with mandatory feeding studies with GM crops (Kuiper, et al. 2013; Ricroch, 2013; Ricroch, et al. 2014). Whether the *in vivo* studies are too short as Seralini suggests, or the inability to define toxicities in because of the extremely low levels of GM material, animal toxicity testing has been problematic. There is ample opportunity for developing new toxicological methods for assessing GM materials (see section on Future Directions).

ALLERGENICITY ASSESSMENT

Food allergies are a popular concern for everyone, even those who are not allergic to as many antigens as their fellow humans. Everyone, to one degree or another, watches what they eat and if any physiological disagreements appear, the first question they ask themselves, "what did I eat?" In a population study of 13,300 subjects, 35% with a mean age of 41 years self-reported that they had adverse reactions to food (Zuberbier, 2004). The incidence, since it is self-reporting, is likely high but it does indicate that people pay attention to how they respond to food. In reality, the actual incidence of food allergy is less than 10% in the human population and is likely to be around 4%. For adults, an often-quoted food allergen is shellfish, which has only a 2% incidence (Sicherer, 2010). While food allergies occur, they are not the dreaded scourge that one would think based on the frequency the subject comes up in casual conversation. Food allergies could very well be the number two most popular conversational topic after the weather.

Even though food allergies occur at a low incidence, it is, nonetheless, important to know if and how GE food and crops may contribute to the overall food allergy frequency. Creating GE crops is not without a purpose or intended function. GM plants are developed to resist insects, be more tolerant to herbicides, and to avoid viral attacks. Most of these intended functions of GM is the creation of proteins. While that may not be the case in the future, GM of plants, especially those with stacked genes, will always have the potential to cause allergies.

The genes, which are transferred to plants so they can be insect resistant and herbicide tolerant, are genes that code for proteins (Goodman, 2011). In the case of insect resistance, the transferred gene codes for an insecticidal protein (Song, 2014). For herbicide tolerance, the transferred gene codes for an enzyme-like protein similar to a protein found in bacteria that allows bacteria to survive exposure to the herbicide. Protecting a crop against a virus requires introducing a gene that codes for antisense RNA (iRNA), which blocks the viral infection (Goodman, 2011).

GE foods and crops are vehicles for introducing new proteins into the human food chain and proteins, whether new, old, or modified, have the potential of eliciting an immune system-mediated allergic response. Consequently, assessing the allergenicity potential of GE food and crops is an essential part of the risk assessment process, and the procedure for defining the toxicity of the new protein being incorporated into the GE food or crop. The initial description for assessing a GE food or crop was promulgated by the Codex Alimentarius Commission; however, there have been useful explanations and guidance provided by numerous sources allowing a toxicologist to make a comprehensive assessment of allergenicity of a GE food and crop (Goodman, 2008a, 2008b, 2013; Delaney, 2008; Verhoeckx, 2016; EFSA Panel on genetically Modified Organisms [GMO Panel] 2010; Poulsen, 2004; Panda, et al. 2013).

In addition to the published regulatory mandates and the various guidance documents that support the requirements, there are publications of specific studies that give insight into the practical implementation of the evaluation steps associated with allergenic assessments. These published studies cover a wide range of investigations that include *in vivo* animal studies, *in vitro* studies, and *ex vivo* investigations. Many of the *in vivo* investigations conform to the EU requirement of using WF as the test article. However, these exemplary allergenicity investigations have the additional benefit of examining the expressed proteins resulting from GE food and crops.

FUTURE DIRECTIONS

The current paradigm used for assessing the hazards associated with GE foods and crops is a two-tier system:

Tier I—Identification of a Potential Hazard

- History of use
- Comparison of existing protein databases (bioinformatics)
- Mechanism of action of associated/related protein toxins
- Information on the degradation of the protein in the digestive tract
- Establish the level of protein in GE food and crop

Tier II—Characterizing the Hazard of the Transgenic Protein

- Acute toxicity
- Repeated dose toxicity testing
- Specialized/tailored studies (hypothesis testing)

This paradigm gives structure and organization for a set of existing tools and capabilities (Delaney, 2008). In addition, the generalized structure of the Two-Tier approach can be expanded to include *in silico* analyses beyond existing databases (bioinformatics universe) to compare homologies, which then can be related to specific toxicities (Mishra, 2012).

All of the components, whole animal testing, bioinformatics, and *in silico* connections were brought together to determine what, if any, additional whole animal testing would be necessary to more accurately assess the health risks associated with GE foods and crops (Ricroch, 2013). Ricroch used the data from high-throughput "-omics" comparisons between 60 GE crops and their non-GE counterparts. These 60 "-omics" comparisons were then compared to 17 chronic (longer than 90-day) toxicity testing studies and 16 reproductive toxicity studies. The comparison of the "-omics" data to the *in vivo* studies was more than informative—it was astonishing!

The "-omics" analysis of GE products resulted in several unexpected results. Conventional plant breeding techniques had a greater effect on gene expression than GE crops. In addition, environmental conditions, such as agricultural practices, field location along with the growing conditions, and the timing when the sampling occurred, had a greater influence on the plants than any GM action. None of the "-omics" comparisons revealed any additional information on hazards or toxicities than what was in hand from the existing 90-day toxicity testing and reproductive studies. Ricroch concludes, and rightly so, that there is nothing to gained by chronic or life-time toxicology studies. Furthermore, the claims and furor raised by the Séralini et al. study (Séralini et al. 2012) that toxicity feeding studies longer than 90-days are necessary for GE crops are without justification and merit.

The Séralini et al. and Ricroch scenario brings into focus an issue bigger than GE food and crops. Ricroch's analysis highlights the value of a structured framework for defining health

hazards (toxicity) using bioinformatics, *in silico* analyses and minimal and only necessary *in vivo* testing. Consequently, the checklist approach for whole animal toxicity testing is finding its way to the graveyard thanks to the evolutionary development of GE foods. The structured framework using toxicology, as a scientific endeavor, and regulatory agencies, as the surrogate for society, can arrive at the correct level and type of testing to allow efficient development of GE foods and crops.

SUMMARY

- GE and breeding are different ways to achieve the same objective.
- A society's attitude toward technologies range from acceptance of their safe development and utilization and support of the new technologies to technophobia.
- Whatever a society's attitude toward technology, it is reflected in the regulations that govern the technology.
- GE foods and crops present a heretofore unseen, or at least very rare, phenomenon: a potential toxin designed to generate a second potential toxin and both potentially expressing toxicity simultaneously.
- There is no evidence that GE food or crops present a human health risk.
- In spite of the urge to search for what may not exist, there is no justification for animal testing for GE foods and crops beyond subchronic testing that is part of a bioinformatics and *in silico* assessment framework.

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16 Oversight Regulations

Robin C. Guy

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INTRODUCTION

Toxicology and safety assessment studies conducted in support of a regulatory submissions for pharmaceuticals, food and feed ingredients, medical devices, pesticides, tobacco products, chemicals, and some consumer products may follow many regulations and guidelines to be acceptable to regulatory bodies. If the studies are not considered adequate, they may not be accepted as part of submission for research or marketing. In addition, there are supporting areas, laboratories, and procedures that may also be required to follow regulations and guidelines. Many of these regulations and guidelines are discussed in this chapter, with a focus on the needs of the United States Food and Drug Administration (FDA).

GOOD LABORATORY PRACTICE REGULATIONS

For those who conduct nonclinical studies to support an application to a federal agency, Good Laboratory Practices, or GLP(s), is first and foremost the primary regulation. GLPs help ensure that studies are conducted in a manner that assures quality and integrity of the data. GLPs focus on major parts of a study, the facility where the work is conducted, and the people conducting the work.

One of the goals for conducting a study according to GLPs is that everything that is done in a study is documented and archived, so that years later, anyone can go through the data and reconstruct the study exactly the way it occurred originally. GLPs concern more than just documentation. They are also used to help plan, conduct, report, and archive a study. There are many parts of the study, which need planning in advance, and are addressed in the study protocol (or study plan, if referring to an OECD study) and Standard Operating Procedures (SOPs).

GLPs are a law in the United States and other countries where the national monitoring authority has mandated as such, and a guideline in many other countries (Table 16.1). Table 16.1 does not include a list of non-US countries with their own unique GLPs.

The OECD has established the Mutual Acceptance of Data (MAD) system in OECD member countries for the mutual acceptance of non-clinical safety study data. Therefore, any OECD Member country may accept studies for submission from laboratories based in other member countries.

TABLE 16.1
International GLP Examples

Country	Agency	Title
USA	FDA	21 CFR 58 Good Laboratory Practice For Nonclinical Laboratory Studies
	EPA	40 CFR 160 Good Laboratory Practice Standards Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
	EPA	40 CFR 792 Good Laboratory Practice Standards Toxic Substances Control Act (TSCA)
International	Specific OECD[a] Member Countries	OECD Principles of GLP and OECD guidelines

[a] OECD = Organisation for Economic Cooperation & Development.

The United States government has promulgated three sets of GLPs for different agencies. The United States FDA has one set of GLPs for products regulated by the FDA. These include:

- Pharmaceuticals
- Biological products
- Veterinary drugs
- Food additives
- Feed additives
- Color additives
- Medical devices
- Electronic products

The FDA GLPs Final Rule went into effect in 1979; with a revised Final Rule that went into effect in 1987. At the time of writing this chapter, a Proposed Notice of Rule Making for GLPs was published by the FDA in the Federal Register in August 2016. This is still outstanding. As it is unclear what will be accepted, changed, or deleted after the comment period. This chapter will not discuss the proposed changes.

The US Environmental Protection Agency (EPA) has two sets of GLPs to suit the needs of two different specific Acts. The EPA GLPs Final Rules went into effect in 1983; with a revised Final Rule that went into effect in 1989. These two are basically identical to each other and the FDA GLPs, with differences due to verbiage due to the specialization of the studies and products. The two Acts are as follows:

- 40 CFR 160; Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- 40 CFR 792; Toxic Substances Control Act (TSCA)

There was a Proposed Notice of Rule Making back in 1999 that combined the two EPA GLPs; however, this combination was never finalized.

Most of the wordings of the GLPs are similar for the FDA, EPA, and OECD. The Scope of each of the previously mentioned GLPs are slightly different and are stated in Table 16.2.

Some differences in wording appear in the FDA, EPA, and OECD versions of the GLPs, but they all refer to the same things. For example, the nomenclature for the material that is being tested for toxicity is different as detailed in Table 16.3.

One other important nomenclature difference is the document that details how a study is run is called a *study protocol* for the FDA and EPA, and a *study plan* for OECD.

TABLE 16.2
GLP Scope

GLP	Scope
US FDA 21 CFR 58	Sec. 58.1 (a) This part prescribes good laboratory practices for conducting nonclinical laboratory studies that support or are intended to support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, animal food additives, human and animal drugs, medical devices for human use, biological products, and electronic products. Compliance with this part is intended to assure the quality and integrity of the safety data filed pursuant to sections 406, 408, 409, 502, 503, 505, 506, 507, 510, 512-516, 518-520, 706, and 801 of the Federal Food, Drug, and Cosmetic Act and sections 351 and 354-360F of the Public Health Service Act. (b) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.
US FIFRA: 40 CFR 160	**Sec. 160.1 Scope.** (a) This part prescribes good laboratory practices for conducting studies that support or are intended to support applications for research or marketing permits for pesticide products regulated by the EPA. This part is intended to assure the quality and integrity of data submitted pursuant to sections 3, 4, 5, 8, 18 and 24(c) of the ***Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA),*** as amended (7 U.S.C. 136a, 136c, 136f, 136q and 136v(c)) and sections 408 and 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 346a, 348). (b) This part applies to any study described by paragraph (a) of this section which any person conducts, initiates, or supports on or after October 16, 1989.
US TSCA: 40 CFR 792	**Sec. 792.1 Scope.** (a) This part prescribes good laboratory practices for conducting studies relating to health effects, environmental effects, and chemical fate testing. This part is intended to ensure the quality and integrity of data submitted pursuant to testing consent agreements and test rules issued under section 4 of *the* ***Toxic Substances Control Act (TSCA)*** (Pub. L. 94-469, 90 Stat. 2006, 15 U.S.C. 2603 et seq.). (b) This part applies to any study described by paragraph (a) of this section which any person conducts, initiates, or supports on or after September 18, 1989. (c) It is EPA's policy that all data developed under Section 5 of TSCA be in accordance with provisions of this part. If data are not developed in accordance with the provisions of this part, EPA will consider such data insufficient to evaluate the health and environmental effects of the chemical substances unless the submitter provides additional information demonstrating that the data are reliable and adequate.
OECD	Section I (1) These Principles of Good Laboratory Practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment. Non-clinical health and environmental safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field. Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

It is important to note that there are a lot of gray areas in the GLPs and being exposed to the written regulations may not be enough to understand what inspectors seek. Training, participation in seminars, and reading FDA warning letters are some of the ways to get the current thinking on GLPs. Remember that in the USA, GLPs are a law, and falsifying data or any records in a study or a report may be a criminal offense.

TABLE 16.3
Test Material Reference

Organization	Nomenclature
FDA	Test and Control Article
EPA	Test, Control and Reference Substance
OECD	Test and Reference Item

The following represent part of the FDA GLPs. The EPA and OECD GLPs are fundamentally similar.

Personnel are the most critical factor in GLPs, as they are the ones to plan, carry out, manage, direct, report, and archive the study. It is up to personnel to master the GLPs and learn their own laboratory's standard operating procedures (SOPs) and study protocols. Personnel must maintain summaries of training (including GLP training) and keep a current job descriptions and curriculum vitae or résumé on file. Laboratory personnel must fulfill their GLP responsibilities for the success of the study.

One item that is overlooked is that the Sponsor of the studies does have GLP responsibilities. Therefore, Sponsors also need GLP training and awareness. Included in their responsibilities is the requirement to provide the test article and characterization information.

Management is critical to the success of the GLP studies also. Responsibilities of management include:

- Assign and replace Study Directors
- Establishment and support of the Quality Assurance Unit (QAU), including assuring that any deviations that are reported by the QAU are communicated to the Study Directors and resolved
- Assure that test and control articles or mixtures are appropriately tested for identity, strength, purity, stability, and uniformity
- Provide required study personnel, resources, facilities, equipment, and materials, and provide training so that personnel can do their assigned jobs
- Review and approve protocols and SOPs

The Study Director is the single point of control in a study. Each study only has one Study Director. They should be aware and be kept aware of any issues in a study. They do need to be kept immediately apprised of any problems that may affect the quality and integrity of the study so that it may be addressed immediately. The Study Director will also:

- Assure the protocol and any amendments have been properly approved and are followed.
- Assure that all data are accurately recorded and verified.
- Assure that all data are collected according to the protocol and SOPs.
- Assure that study personnel are familiar with and adhere to the study protocol and SOPs.
- Assure that study data are transferred to the archives at the close of the study.

The QAU monitors significant study events and facility operations, reviews records and reports, and assures management of GLP compliance. For any given study, the QAU is entirely separate from and independent of the personnel engaged in the conduct and direction of that study. QAU activities including, but not limited to

- Maintain the master schedule.
- Maintain copies of all protocols and amendments.
- Schedule inspections and audits.

- Inspect each nonclinical laboratory study at adequate intervals to assure the integrity of the study, report findings to Management and the Study Director, and maintain records of each inspection.
- Immediately notify the Study Director and Management of any problems that are likely to affect the integrity of the study.
- Submit periodic status reports on each study to the Study Director and Management.
- Review the final study report.
- Prepare the QA Statement to be included in the final report that specifies the dates inspections were made and findings reported to Management and to the Study Director.

The facilities must be of adequate size and design. There needs to be separate and appropriate areas for the receipt, storage, mixing, and handling of the test and control articles. Separation of areas is critical for the elimination of possible contamination. All computerized operations and archived computer data need to be housed under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces). The heating, ventilation, and air conditioning system design and maintenance, need to be documented, including filter changes. Temperature and humidity (as appropriate) monitoring must be conducted in critical areas, including refrigerators, freezers, ovens, and so on.

Equipment must be appropriately designed and of adequate capacity. Equipment is maintained and operated in a manner that ensures valid results. There needs to be SOPs and/or operating manuals for all equipment, including maintenance schedules and logs, and if appropriate, standardization/calibration procedures, schedules, and logs.

Since computers are considered equipment, the following procedures need to be in place and need to be documented:

- Validation study, including validation protocol/plan and documentation of the protocol/plan's completion
- Maintenance of equipment, including storage capacity and back-up procedures
- Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change
- Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer
- Procedures for emergency back-up of the computer system (e.g., back-up battery system and data forms for recording data in the event of a computer failure or power outage)

The FDA does want to ensure that the equipment/software is Part 11 compliant (21CFR58.11).

Testing Facility Operations are also critical to how a study is conducted. The laboratory must follow written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data. There must be a historical file of outdated or modified SOPs, personnel records, and computer programs and files.

Reagents and solutions are addressed in the GLPs to ensures the quality of reagents at the time of receipt and subsequent use.

Animal care and housing must be adequate to minimize stress and uncontrolled influences that could alter the response of test system to the test article. The animal room(s) housing the study, cages, feeders, waterers, and so on must be cleaned and sanitized on a regular basis. There needs to be SOPs covering environment, housing, feeding, handling, and care of laboratory animals, and that the SOPs and the protocol must be followed. Pest control procedures need to be documented, especially any use of chemicals.

All newly received animals need to be appropriately isolated, identified, and their health status is evaluated. Any treatment given to animals that become diseased needs to be authorized by the Study Director and documented. Animals of different species, or animals of the same species on

different projects, must be housed separately to avoid contamination. Feed and water samples need to be collected at appropriate sources, analyzed periodically, and analytical documentation is maintained with the facility records.

Since the test and control articles are being tested for safety, these must be characterized, and stability determined to ensure that they are acceptable for the length of the study. The responsibility for carrying out appropriate characterization and stability testing may be assumed by the facility performing the study or by the study Sponsor. When test article characterization and stability testing is performed by the sponsor, the test facility receives documentation that this testing has been conducted in a timely manner. Procedures must be in place at the facility to ensure that:

- The acquisition, receipt and storage of test articles, and means used to prevent deterioration and contamination are as specified.
- The identity, strength, purity, and composition (i.e., characterization) to define the test and control articles are determined for each batch and are documented.
- The stability of test and control articles is documented.
- The transfer of samples from the point of collection to the analytical laboratory is documented.
- Storage containers are appropriately labeled and assigned for the duration of the study.
- Reserve samples of test and control articles for each batch are retained for studies lasting more than four weeks.
- The distribution of these materials is documented.
- Proper identification and storage.
- Precluding contamination, deterioration, or damage during

In many GLP studies, the test article needs to be mixed with a carrier or a vehicle for ease of dosing. The mixtures of test articles with carriers also need analytical testing to determine uniformity of mixtures and to determine periodically the concentration of the test or control article in the mixture, and to determine the stability as required under study conditions. It is critical that the analytical results are reported to the Study Director in a timely manner.

Study protocols must be properly written and authorized, and studies are conducted in accordance with the protocol and SOPs. The GLPs have a list of what must be contained in the protocol, and the Study Director provides their scientific and regulatory expertise to determine other needed information. Laboratory personnel then conduct the study according to the protocol. Each protocol may be different, and it is a good idea to have a protocol review meeting with the appropriate people in attendance, so that the Study Director can go over any nuances with the laboratory personnel. Any changes, revisions, or amendments to the protocol must be authorized/acknowledged, signed, and dated by the Study Director.

As mentioned earlier, each nonclinical laboratory study must conform with protocol and SOP requirements. Activities that are taken into account while conducting studies include:

- Test system monitoring
- Recording of raw data (manual and automated)
- Corrections to raw data (corrections must not obscure the original entry and must be dated, initialed, and explained)
- Randomization of test systems (what you're testing the test article on, e.g., animals, bacteria, cell cultures)
- Collection and identification of specimens

SOPs for collecting and recording data need to be present to help guide personnel on the proper way to document. There must be enough data recorded so that the study may be reconstructed years

down the line. For each study, the quality and integrity of the data is critical. Documentation procedures should ensure that data are:

- *Attributable*: The raw data can be traced by date and signature or initials of the individual observing and recording the data. Should more than one individual observe or record the data, that fact should be reflected in the data.
- *Legible*: The raw data are readable and recorded in a permanent medium. If changes are made to original entries, the changes
  - Must not obscure the original entry.
  - Indicate the reason for change.
  - Must be signed or initialed and dated by the person making the change.
- Contemporaneous: The raw data are recorded at the time of the observation.
- *Original*: The first recording of the data.
- *Accurate*: The raw data are true and complete observations. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or retain with the study records a written explanation stating reasons for any empty fields.

After the study is conducted, it must be reported out, even if the study was terminated early. The GLPs contain a listing of items that are to be included in each study report. QAU will audit the reports. These reports and any amendments, must be signed by the Study Director.

The test facility must also store and retrieve raw data, documentation, protocols, final reports, and specimens according to the GLPs. These items are stored in the Archive and remain there for a specific amount of time. They remain the proof that the study was conducted according to GLPs and help support the quality and integrity of the study and data. The following is important to incorporate into the practices of the Archive:

- Retain all appropriate raw data, documentation, protocols, final reports, and specimens.
- Identify an individual responsible for the archives. This is the Archivist. Other individuals may be hired to assist in maintaining the archives.
- Index archived material are retained or referred to in the archives to permit expedient retrieval. This also includes electronic records.
- If there are any raw data or specimens retained in another, possible off-site, archive location, the archives index must make specific reference to those other locations.
- Access to the archives must be controlled.
- Ensure that the environmental controls need to minimize deterioration.
- Incorporate controlled procedures for adding or removing material from the archives.

21 CFR PART 11

The FDA's 21 CFR Part 11 (Part 11) describes the technical and procedural requirements that must be met for the use of electronic records and electronic signatures. It establishes requirements for record content, signing, and retention.

If a firm is keeping electronic records or using electronic signatures, they may need to be compliant with 21 CFR Part 11 so that the electronic records and signatures are an exact copy, authentic, dependable, secure, and equivalent to paper records and handwritten signatures. However, it is pertinent to review the regulation, as there are quite a few exceptions to sift through. As of this writing, A Guidance for Industry Part 11, Electronic Records; Electronic Signatures—Scope and Application is the latest word. It became effective in August of 2003 and reflects the FDA's current thinking on the subject.

According to the Guidance, the FDA will enforce specific Part 11 requirements (although enforcement of some legacy systems, under certain circumstances, will be broader). The FDA intends to enforce all other provisions of Part 11 including, but not limited to, certain controls for

closed systems in § 11.10. For example, the FDA intends to enforce provisions related to the following controls and requirements:

- Limiting system access to authorized individuals
- Use of operational system checks
- Use of authority checks
- Use of device checks
- Determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- Establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- Appropriate controls over systems documentation
- Controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- Requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)
- Requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30)

The Agency also expects that persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules. The EPA also has predicate rules, which may be found in 40CFR Part 160.

ANIMAL RULE

Nonclinical studies to support drug and biological product approvals by the FDA are usually followed by clinical trials if the Sponsor is successful getting an Investigational New Drug (IND) approved by the Agency. However, there may be times when human efficacy studies are not ethical and field trials after an accidental or deliberate exposure are not feasible. The regulations that set forth the pathway for approval of these products under 21 CFR 314.600 through 314.650 (drugs) or 21 CFR 601.90 through 601.95 (biological products) are commonly referred to as the Animal Rule. The FDA also published a *Guidance for Industry: Product Development Under the Animal Rule* in October 2015, which describes the Agency's current thinking on a topic.

As described in the Scope of the Animal Rule, "... it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance....". The Animal Rule states that for drugs developed to ameliorate or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic substances, when human efficacy studies are not ethical and field trials are not feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans. Drugs evaluated for efficacy under the Animal Rule should be evaluated for safety under the existing requirements for establishing the safety of new drugs. The Animal Rule states that the FDA will rely on evidence from animal studies to provide substantial evidence of effectiveness only when all of the following four criteria are met:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product
2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans
3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity
4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

If all these criteria are met, it is reasonable to expect the effectiveness of the drug in animals to be a reliable indicator of its effectiveness in humans. However, prior to planning a program utilizing the Animal Rule, consult the FDA, as the FDA will determine whether the previously noted criteria have been met and the Animal Rule can be used.

ANIMAL CARE AND WELFARE

Critical to conducting quality studies is animal care and animal welfare. Laboratory animals have welfare protection under the US law. It is imperative that animals be treated humanely with the best possible care. Animals need to be taken care of, including being provided with fresh food and water, shelter, environmental enrichment, and veterinary care when needed. Animals also need our respect. Animal welfare needs to be the first thing that people working with animals should think about, so that the study is designed properly from the start, and the facility is able to handle the animals on the study.

The Animal Welfare Act (AWA) requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, transported commercially, or exhibited to the public. The requirements of the AWA are set forth under the Regulations and Standards in 9CFR Chapter 1, Subchapter A. It details the responsibilities and functions of roles (such as Attending Veterinarian, Institutional Office, Principal Investigators and Institutional Animal Care and Use Committee [IACUCs]), training and personnel qualifications, annual reporting, or to the housing and care of animals (such as feeding and environmental enhancement for nonhuman primates and exercise for dogs).

Note that the definition of the Principal Investigator in the AWA is different from the Principal Investigator in the OECD GLPs (Table 16.4). Care must be taken in laboratories the further define these titles to avoid mix-ups.

The Chief Executive Officer of the research facility shall appoint an IACUC for that facility, qualified through experience and expertise of its members to assess the research facility's animal program, facilities, and procedures. The IACUC will review protocols and procedures (both current and proposed) and look for areas of noncompliance with the AWA. They will also inspect the research facility and review personnel qualifications and training. They also prepare reports of the evaluations conducted and submit them to the CEO of the facility.

The Guide for the Care and Use of Laboratory Animals is a valuable resource that is followed by laboratories. The purpose of the Guide for the Care and Use of Laboratory Animals (the Guide) is to assist institutions in caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate. The Guide is also intended to assist investigators in fulfilling their obligation to plan and conduct animal experiments in accord with the highest scientific, humane, and ethical principles.

The eighth edition of the Guide is divided into five chapters.

- Chapter 1 presents key concepts, including the goals and intended audiences of the Guide as well as terminology. It also emphasizes a commitment to the concepts of the Three R's (Replacement, Reduction, and Refinement) and provides an enhanced discussion of the ethics of animal use and investigator/institutional obligations.

TABLE 16.4
Principal Investigator Definitions

Standard	Definition
US Animal Welfare Act	An employee of a research facility, or other person associated with a research facility, responsible for a proposal to conduct research and for the design and implementation of research involving animals
Organisation for the Economic Cooperation and Development	The Principal Investigator acts on behalf of the Study Director for the delegated phase and is responsible for ensuring compliance with the Principles of GLP for that phase

- Chapter 2 focuses on the overall institutional animal care and use program. It takes into account institutional policies and responsibilities, regulatory considerations, programs and personnel management (including training and occupational health and safety), in addition to discussions on the IACUC.
- Chapter 3 focuses on the animals and provides recommendations for housing and environment, including social housing, environmental enrichment, animal well-being, and scientific validity.
- Chapter 4 focuses on veterinary care and the responsibilities of the attending veterinarian.
- Chapter 5 focuses on the facility itself.

The Guide has recommendations for the size of housing for laboratory animals. The most recent version of the Guide increases the size required for rodents, which is a significant expense for laboratories (Table 16.5). In addition, recommended minimum space for rabbits and dogs are in Table 16.6. Table 16.7 includes recommended space for nonhuman primates. European or other countries may have different requirements for animal housing.

TABLE 16.5
Recommended Minimum Space for Commonly Used Laboratory Rodents Housed in Groups

Animals	Weight, g	Floor Area/Animal[a] in.² (cm²)	Height[b] in. (cm)	Comments
Mice in groups[c]	<10	6 (38.7)	5 (12.7)	Larger animals may require more space to meet the performance standards.
	Up to 15	8 (51.6)	5 (12.7)	
	Up to 25	12 (77.4)	5 (12.7)	
	>25	>15 (>96.7)	5 (12.7)	
Female + litter		51 (330) (recommended space for the housing group)	5 (12.7)	Other breeding configurations may require more space and will depend on considerations such as number of adults and litters, and size and age of litters.[d]
Rats in groups[c]	<100	17 (109.6)	7 (17.8)	Larger animals may require more space to meet the performance standards.
	Up to 200	23 (148.35)	7 (17.8)	
	Up to 300	29 (187.05)	7 (17.8)	
	Up to 400	40 (258.0)	7 (17.8)	
	Up to 500	60 (387.0)	7 (17.8)	
	>500	>70 (>451.5)	7 (17.8)	
Female + litter		124 (800) (recommended space for the housing group)	7 (17.8)	Other breeding configurations may require more space and will depend on considerations such as number of adults and litters, and size and age of litters.[d]
Hamsters[c]	<60	10 (64.5)	6 (15.2)	Larger animals may require more space to meet the performance standards.
	Up to 80	13 (83.8)	6 (15.2)	
	Up to 100	16 (103.2)	6 (15.2)	
	>100	>19 (>122.5)	6 (15.2)	
Guinea pigs[c]	Up to 350	60 (387.0)	7 (17.8)	Larger animals may require more space to meet the performance standards.
	>350	>101 (>651.5)	7 (17.8)	

[a] Singly housed animals and small groups may require more than the applicable multiple of the indicated floor space per animal.

[b] From cage floor to cage top.

[c] Consideration should be given to the growth characteristics of the stock or strain as well as the sex of the animal. Weight gain may be sufficiently rapid that it may be preferable to provide greater space in anticipation of the animal's future size. In addition, juvenile rodents are highly active and show increased play behavior.

[d] Other considerations may include culling of litters or separation of litters from the breeding group, as well as other methods of more intensive management of available space to allow for the safety and well-being of the breeding group. Sufficient space should be allocated for mothers with litters to allow the pups to develop and wean without detrimental effects on the litter.

TABLE 16.6
Recommended Minimum Space for Rabbits and Dogs Housed in Pairs or Groups

Animals	Weight[a] kg	Floor Area/Animal[b] ft² (m²)	Height[c] in. (cm)	Comments
Rabbits	<2	1.5 (0.14)	16 (40.5)	Larger rabbits may require more cage height to allow animals to sit up.
	Up to 4	3.0 (0.28)	16 (40.5)	
	Up to 5.4	4.0 (0.37)	16 (40.5)	
	>5.4[c]	>5.0 (>0.46)	16 (40.5)	
Dogs[e]	<15	8.0 (0.74)	—[f]	Cage height should be sufficient for the animals to comfortably stand erect with their feet on the floor.
	Up to 30	12.0 (1.2)	—[f]	
	>30[d]	>24.0 (>2.4)	—[f]	

[a] To convert kilograms to pounds, multiply by 2.2.
[b] Singly housed animals may require more space per animal than recommended for pair- or group-housed animals.
[c] From cage floor to cage top.
[d] Larger animals may require more space to meet performance standards.
[e] These recommendations may require modification according to body conformation of individual animals and breeds. Some dogs, especially those toward the upper limit of each weight range, may require additional space to ensure compliance with the regulations of the Animal Welfare Act. These regulations mandate that the height of each cage be sufficient to allow the occupant to stand in a *comfortable position* and that the minimal square feet of floor space be equal to the "mathematical square of the sum of the length of the dog in inches (measured from the tip of its nose to the base of its tail) plus 6 inches; then divide the product by 144."
[f] Enclosures that allow greater freedom of movement and unrestricted height (i.e., pens, runs, ls) are preferable.

TABLE 16.7
Recommended Minimum Space for Nonhuman Primates Housed in Pairs or Groups

Animals	Weight[a] kg	Floor Area/Animal[b] ft² (m²)	Height[c] in. (cm)	Comments
Monkeys[d] (including baboons)				Cage height should be sufficient for the animals to comfortably stand erect with their feet on the floor. Baboons, patas monkeys, and other longer-legged species may require more height than other monkeys, as might long-tailed animals and animals with prehensile tails. Overall cage volume and linear perch space should be considerations for many neotropical and arboreal species. For brachiating species cage height should be such that an animal can, when fully extended, swing from the cage ceiling without having its feet touch the floor. Cage design should enhance brachiating movement.
Group 1	Up to 1.5	2.1 (0.20)	30 (76.2)	
Group 2	Up to 3	3.0 (0.28)	30 (76.2)	
Group 3	Up to 10	4.3 (0.4)	30 (76.2)	
Group 4	Up to 15	6.0 (0.56)	32 (81.3)	
Group 5	Up to 20	8.0 (0.74)	36 (91.4)	
Group 6	Up to 25	10 (0.93)	46 (116.8)	
Group 7	Up to 30	15 (1.40)	46 (116.8)	
Group 8	>30[e]	>25 (>2.32)	60 (152.4)	
Chimpanzees (*Pan*)				For other apes and large brachiating species cage height should be such that an animal can, when fully extended, swing from the cage ceiling without having its feet touch the floor. Cage design should enhance brachiating movement.
Juveniles	Up to 10	15 (1.4)	60 (152.4)	
Adults[f]	>10	>25 (>2.32)	84 (213.4)	

[a] To convert kilograms to pounds, multiply by 2.2.
[b] Singly housed primates may require more space than the amount allocated per animal when group housed.
[c] From cage floor to cage top.
[d] Callitrichidae, Cebidae, Cercopithecidae, and Papio.
[e] Larger animals may require more space to meet performance standards.
[f] Apes weighing over 50 kg are more effectively housed in permanent housing of masonry, concrete and wire-panel structure than in conventional caging.

There are also non-governmental organizations for example: the American Association for Laboratory Animal Science (AALAS) and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

AALAS (www.aalas.org) is an association of professionals that advances responsible laboratory animal care and use to benefit people and animals

AAALAC (www.aaalac.org) is a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs.

OCCUPATIONAL HEALTH AND SAFETY

Regulations are also promulgated to protect laboratory workers. All laboratory personnel must have a safe working environment and must be educated of the potential hazards associated with their jobs. In the US, the Occupational Safety and Health Administration (OSHA) has regulations that are applicable to laboratory environments. These are codified in the CFR (29 CFR1910.1200). The regulations cover aspects of hazardous materials in the workplace, including information on Safety Data Sheets (SDS), labeling and signage, and training.

Most of the studies that are performed for nonclinical toxicology assessments have little or no history of safety in humans. Therefore, precautions need to be taken to limit or eliminate the exposure to the chemicals.

Employees need a means to find information about the hazards associated with any material in their workplace. When available, SDS are good resources that summarize information about the hazards, handling procedures, emergency first aid, and required personal protective equipment (PPE) regarding each substance. It is important to note that not many toxicology study test materials will have a SDS, but the laboratory should have them for reagents, solvents, cleaning agents, anesthetic agents, and other commercially available chemicals used in the laboratory.

All laboratories need to have provisions for appropriate PPE. 21CFR1910.120 discusses levels of protection and protective gear, and PPE test methods.

21CFR1910.120 also discusses general environmental conditions, and OSHA's Bloodborne Pathogens Standard is on 29CFR 1910.1030. The standard's requirements state what employers must do to protect workers who are occupationally exposed to blood or other potentially infectious materials (OPIM), as defined in the standard. That is, the standard protects workers who can reasonably be anticipated to come into contact with blood or OPIM as a result of doing their job duties. Many laboratories deal with blood or blood products. Clinical laboratories will analyze human samples. Although not specifically mentioned in this standard, as it focuses on human samples, nonhuman primates are utilized in studies, and there is always a risk of bloodborne pathogens from this animal model. In general, the standard requires employers to establish an exposure control plan. This is a written plan to eliminate or minimize occupational exposures. Employers must update the plan annually to reflect changes in tasks, procedures, and positions that affect occupational exposure, and technological changes that eliminate or reduce occupational exposure. In addition, employers must ensure that their workers receive regular training that covers all elements of the standard including, but not limited to: information on bloodborne pathogens and diseases, methods used to control occupational

Currently, OSHA follows 29CFR Occupational Safety and Health Standards, subpart Z, Standard number 1910.1450 for Occupational exposure to hazardous chemicals in laboratories. This section discusses the Chemical hygiene plan, hazard identification, permissible limits, monitoring, employee information and training, provisions for additional employee protection, recordkeeping, and medical consultation and examinations. Part of 29CFR1910.1450 is Appendix A. Appendix A contains the National Research Council (NRC) Recommendations Concerning Chemical Hygiene in Laboratories (Non-Mandatory). Contained in the Appendix are recommendations from the NRC's Prudent Practices, which deals with both general laboratory safety and many types of chemical

hazards. These also include information on personnel, the facility, the chemical hygiene plan, different types of chemicals, including nanoparticles, safety recommendations, emergency procedures and laboratory security.

Radiation may also be found in a laboratory. For example, test materials may be labeled so that the radiation may be tracked for absorption, metabolism, distribution and excretion studies. Another example may be use of X-rays and other ionizing radiation to ensure placement of catheters or other devices, or to monitor effects in animals. Workers need to take necessary precautions to avoid exposure, and they need to be monitored. These regulations are covered briefly in OSHA regulations but are detailed in the US Nuclear Regulatory Commission regulations.

WASTE DISPOSAL

Laboratories routinely must dispose of waste. Waste can be biological or chemical but may also contain infective agents or radioactive materials. Records must be maintained for disposal of radioactive materials. Waste disposal is regulated at the local, state, and federal levels. In general, much of the laboratory waste may be incinerated. The US Nuclear Regulatory Commission has more detailed information in 10CFR. However, it is important to research the acceptable methods for the disposal of all types of waste products used in the laboratory.

Waste disposal is also managed by the EPA. The EPA publishes a handy manual (EPA, 2000) describing how to handle waste in small laboratories. It includes guidelines covering water discharges, hazardous wastes, nonhazardous solid wastes, biologically active substances and waste, radioactive materials, toxic substances, pesticides, and other aspects of waste handling.

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Appendix I: Selected Regulatory and Toxicological Acronyms

510(k)	Premarket notification for change in a device
AALAS	American Association for Laboratory Animal Science
AAMI	Association for the Advancement of Medical Instrumentation
ABT	American Board of Toxicology
ACGIH	American Conference of Governmental Industrial Hygienists
ACT	American College of Toxicology
ADE	Adverse Drug Event (of drug substances)
ADI	Acceptable Daily Intake
AIDS	Acquired Immune Deficiency Syndrome
AIHA	American Industrial Hygiene Association
AIMD	Active Implantable Medical Device
ANDA	Abbreviated New Drug Application
ANSI	American National Standards Institute
APHIS	Animal and Plant Health Inspection Service
ARFD	Acute Reference Dose
ASTM	American Society for Testing and Materials
CAS	Chemical Abstract Service
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Drug Evaluation and Research (FDA)
CE	Conformité Européene (European Conformity)
CDRH	Center for Devices and Radiological Health (FDA)
CFAN	Center for Food and Nutrition (FDA)
CFR	*Code of Federal Regulations*
CIIT	Chemical Industries Institute of Toxicology
CNS	Central Nervous System
CPMP	Committee on Proprietary Medicinal Products (U.K.)
CRF	Code of Federal Regulations
CRFD	Chronic Reference Dose
CSE	Control Standard Endotoxin
CSM	Committee on Safety of Medicines (U.K.)
CTC	Clinical Trial Certificate (U.K.)
CTD	Common Technical Document
CTX	Clinical Trial Certificate Exemption (U.K.)
CVM	Center for Veterinary Medicine (FDA)
DART	Developmental and Reproduction Toxicology
DHEW	Department of Health, Education and Welfare (no longer existent)
DHHS	Department of Health and Human Services
DIA	Drug Information Associates
DMF	Drug (or Device) Master File
DSHEA	Dietary Supplement Health and Education Act
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries Association
EM	Electron Microscopy
EMC	Electromagnetic Compatibility

(*Continued*)

EPA	Environmental Protection Agency
EU	European Union
FCA	Freund's Complete Adjuvant
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
FDLI	Food and Drug Law Institute
FIFRA	Federal Insecticides, Fungicides, and Rodenticides Act
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GPMT	Guinea Pig Maximization Test
HIMA	Health Industry Manufacturers Association
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICH	International Conference on Harmonization
id	Intradermal
IDE	Investigational Device Exemption
IND(A)	Investigational New Drug Application
INN	International Nonproprietary Names
ip	Intraperitoneal
IRAG	Interagency Regulatory Alternatives Group
IRB	Institutional Review Board
IRLG	Interagency Regulatory Liaison Group
ISO	International Standards Organization
IUD	Intrauterine Device
iv	Intravenous
JECFA	Joint Expert Committee for Food Additives
JMAFF	Japanese Ministry of Agriculture, Forestry, and Fishery
JPMA	Japanese Pharmaceutical Manufacturers Association
LA	Licensing Authority (U.K.)
LAL	*Limulus* amebocyte lysate
LD_{50}	Lethal dose 50: The dose calculated to kill 50% of a subject population, median lethal dose
LOEL	Lowest observed effect level
MAA	Marketing Authorization Application (EEC)
MCA	Medicines Control Agency
MD	Medical device
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor & Welfare (Japan)
MID	Maximum implantable dose
MOA	Mode of Action
MOE	Margin of Exposure
MOU	Memorandum of Understanding
MRL	Maximum Residue Limits
MSDS	Material Safety Data Sheet
MTD	Maximum tolerated dose
NAS	National Academy of Science
NCTR	National Center for Toxicological Research
NDA	New drug application
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health

(*Continued*)

NK	Natural killer
NLM	National Library of Medicine
NOEL	No observable effect level
NTP	National Toxicology Program
ODE	Office of Device Evaluation
OECD	Organization for Economic Cooperation and Development
PDI	Primary Dermal Irritancy
PDN	Product Development Notification
PEL	Permissible Exposure Limit
PhRMA	Pharmaceutical Research and Manufacturers Association
PL	Produce License (U.K.)
PLA	Produce License Application
PMA	Premarket approval Applications
po	Per os (orally)
PTC	Points to Consider
QAU	Quality Assurance Unit
RAC	Recombinant DNA Advisory Committee
RCRA	Resources Conservation and Recovery Act
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund/Amendments and Reauthorization Act
sc	Subcutaneous
SCE	Sister chromatic exchange
SNUR	Significant New Use Regulations
SOP	Standard Operating Procedure
SOT	Society of Toxicology
SRM	Standard Reference Materials (Japan)
STEL	Short Term Exposure Limit
TLV	Threshold limit value
USAN	United States Adopted Name Council
USDA	US Department of Agriculture
USEPA	US Environmental Protection Agency
USP	US Pharmacopoeia
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Data Link
WHO	World Health Organization

Appendix II

Notable Regulatory Internet Addresses

Organization or Publication	Web Address (Url)	Sample Main Topics
ABPI	http://www.abpi.org.uk/	
Adverse Reactions Bulletin	http://www.thomsonscience.co	
Agency for Toxic Substances and Disease Registry	www.atsdr.cdc.gov	
Association of Clinical Biochemists	http://www.leeds.ac.uk/acb/	Items of general medical interest and an assay finder to help researcher find methods or labs to measure a wide variety of hormones, metals, enzymes and drugs in body fluids
Australian Therapeutic Goods Administration	http://www.health.gov.au/tga	Medical Devices; GMP Codes; Parliamentary Secretary's Working; Status Document; Party on Complementary medicines; Medical Releases; Publications; Site map; Related Sites
BioMedNet	http://www.cursci.co.uk/BioMedNet/biomed.html/ OR http://www.BioMedNet.com	The world wide web club for the biological and medical community (free membership)
Canadian Health Protection Board	http://www.hwc.ca/hpb	
Canadian Health Protection Branch	http://www.hc-sc.gc.ca/hpb	Medical Devices; Chemical Hazards; Food; Product Safety; Science Advisory Board; Diseases; Radiation Protection; Drugs; HPB Transition Policy, Planning and Coordination
Centre for Medicines Research	http://www.cmr.org/	
ChemInfo	www.indiana.edu/~cheminfo/ca_csti.html	SirCH: Chemical Safety or Toxicology Information
Clinical Pharmacology Drug Monograph Service	http://www.cponline.gsm.com	
Clinician's Computer-Assisted Guide to the Choice of Instruments for Quality of Life Assessment in Medicine	http://www.glamm.com/ql/guide.htm	This contains hypertext with references to QoL measurements divided into (a) general diseases, (b) specific diseases and therapies, (c) health organizations, (d) bibliography.
ClinWeb	http://www.ohsu.edu/clinweb	Oregon Health Sciences University
CNN Interactive (Health)	http://www.cnn.com/HEALTH/index.html	Up-to-date information on health issues including drug safety concerns and withdrawals
Code of Federal Register	http://www.access.gpo.gov/nara/cfr/index.html OR http://www.access.gpo.gov/su_docs/aces/aces140.html	For proposed rules and regulations
Code of Federal Regulations	http://www.access.gpo.gov/nara/cfr/cfr-table-search.html	NARA Code Sections

(*Continued*)

Organization or Publication	Web Address (Url)	Sample Main Topics
Committee on Safety of Medicines (CSM)	http://www.open.gov.uk/mca/csmhome.htm	
Cornell Legal Library	http://www.law.cornell.edu	Code of Federal Regulations; Supreme Court Decisions; U.S. Code; Circuit Courts of Appeal
Current Problems in Pharmacovigilance	http://www.opwn.gov.uk/mca/mcahome.htm	
Cutaneous Drug Reactions	http://triz.dermatology.uiowa.edu/home.html	
DIA Home Page	http://www.diahome.org	Home Page of the Drug Information Association
Doctor's Guide to the Internet	http://www.psigroup.com	
Documents for Clinical Research	http://www.ams.med.unigoettingen.de/~rhilger/Document.html	*Declaration of Helsinki*, other documents and collection of related sites
Druginfonet	http://www.druginfonet.com	
EC DGXIII Telecommunications	http://www.ispo.cec.be/	Information
EMBASE	http://www.healthgate.com/healthGate/price/embase.html	
EPA	www.epa.gov	
Eudra Net: Network Services for the European Union Pharmaceutical Regulatory Sector	http://www.eudra.org	Includes information on the European Agency for the Evaluation of Medicinal Products.
EMEA	http://www.eudra.org/emea.html	
Europa	http://www.cec.lu	Official website of the European Union
European Agency for the Evaluation of Medicinal Products	http://www.eudra.org/en_home.htm	What's New; Documents Forum; Other Sites
European Sites	http://www.eucomed.be/eucomed/links/links.htm	European Institutions; Related Sites
European Pharmacovigilance Research Group	http://www.ncl.ac.uk/~neprg/	
Food and Drug Administration (FDA)	www.fda.gov	Foods; Human Drugs; Biologics; Animal Drugs; Cosmetics; Medical Devices/ Radiological Health
FDA—CBER Center for Biologics Evaluation and Research	http://www.fda.gov/cber	
CBER What's New	http://www.fda.gov/cber/whatsnew.htm	
FDA—CDER Center for Drug Evaluation and Research	http://www.fda.gov/cder	
FDA Adverse Events Database	http://www.fda.gov/cder/adr	
CDER What's New	http://www.fda.gov/cder/whatsnew.htm	
FDA—CDRH	www.fda.gov/cdrh/index.html	Home page
Search site	www.fda.gov/cdrh/search.html	Search CDRH site
Comment	www.fda.gov/cdrh/comment4.html	Comment on CDRH site

(*Continued*)

Organization or Publication	Web Address (Url)	Sample Main Topics
Device Advice	www.fda.gov/cdrh/devadvice/32.html	
PDF Reader	www.fda.gov/cdrh/acrobat.html	
FDA—CFSAN Center for Food Safety and Applied Nutrition	http://vm.cfsan.fda.gov	
FDA—Center for Toxicological Research	http://www.fda.gov/nctr	
FDA—CVM Center for Veterinary Medicine	http://www.fda.gov/cvm	
FDA—Bioengineered food	http:www.fda.gov/oc/biotech/default.htm	
FDA—Breast Implants	http://www.fda.gov/cdrh/breastimplants/index.html	
FDA—Cosmetics	http://vm.cfsan.fda.gov//~lrd/cosmetm.html	
FDA—Dietary Supplements	http://vm.cfsan.fda.gov/~dms/supplmt.html	
FDA's Electronic Freedom of Information Act	http://www.fda.gov/foi/foia2.htm	
FDA—Field Operations	www.fda.gov/ora/	What's New; Import Program; Inspectional, Science and Compliance References; Federal/State Relations
The Common Technical Document for the Registration of Pharmaceuticals for Human use: 08-24-00	http://www.fda.gov/cder/guidance/4022dfts.htm	
Design Controls	www.fda.gov/ora/inspect_ref/qsreq/dcrpgd.html	Design Control Report and Guidance Text
	www.fda.gov/ora/inspect_ref/igs/elec_med_dev/emcl.html	Guide to Inspections of Electromagnetic Compatibility Aspects of Medical Device Quality Systems Text
Guide to Inspections of Quality Systems	www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm	QSIT Inspection Handbook Text
Guide to Inspections of Quality Systems	www.fda.gov/ora/inspect_ref/igs/qsit/QSITGUIDE.PDF	PDF version of QSIT Inspection Handbook Text
Photosafety Testing 07-05-00	http://www.fda.gov/cder/guidance/3281dft.htm	
Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products 06:01:00	http://www.fda.gov/cder/guidance/2887fnl.htm	
FDA—MedWatch	http://www.fda.gov/medwatch/	US FDA drug adverse event reporting system
FDA—Tampons	http://www.fda.gov/oc/opacpm/topicindexes/tampons.html	
Food and Drug Law Institute	http://www.fdli.org	Special Interest; Publications; Multimedia; Order Products; Academic Programs; Directory of lawyers and Consultants; Contact Us

(*Continued*)

Organization or Publication	Web Address (Url)	Sample Main Topics
Health Industry and Manufacturers Association (HIMA)	http://www.himanet.com	About HIMA; Newsletter; HIMA Calendar; Industry Resources; Business Opportunities; FDA/EPA/OSHA; Reimbursement/Payment; Global Year 2000; Government Relations; Public Relations; Small Company; Diagnostics
Health on the Net	http://www.hon.ch	
Health Information on the Internet	http://www.wellcome.ac.uk. healthinfo/	New bimonthly newsletter from the Wellcome Trust and the RSM
Hyppos Project	http://ifinet.it/hypposnet	Information in Italian and English about the Hyppos Project, which has led to the development of a QoL tool for the measurement of hypertensive patients in Italy. It contains a description of the project, the tool, publications about the development of the tool and its application, plus general references to QoL and hypertension
International Classification of Disease (ICD)-10	http://www.cihi.ca.newinit/scope.htm	
International Conference on Harmonization (ICH) 3 Home Page	http://cc.umin.u-tokyo.ac.jp/ich/ich3. html	Official ICH website with documents (needs a password)
ICH documents	http://www.pharmweb.net/pwmirror/ pw9/ifpma/ich1/html	
International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human use	http://www.ifpma.org/ich1.html	
International Federation of Pharmaceutical Manufacturers	http://www.ifpharma.com	ICH documents and postings; International Pharmaceutical issues
International Regulatory Monitor (Monitor)	http://www.go-nsi.com/pubs	Editorial Portion of Newsletter
International Society of Pharmacoepidemiology	http://www.pharmacoepi.org	
Internet Grateful Med	www.igm.nlm.nih.gov	
InterPharma	http://www.interpharma.co.uk	The latter are vast sites with links to other databases for pharmaceutical support sites—http://www.MedsiteNavigator.com
JAMA	http://www.ama-assn.org/jama	This gives many other useful USA sites
Japanese Ministry of Health and Welfare	http://www.mhw.go.jp/english/ index.html	Organization; Y2K Problem; Statistics; White Paper; Related Sites
Library of Congress	http://thomas.loc.gov	Searchable database of federal legislation, Congressional Record and committee information
Market and Exploitation of Research	http://www.cordis.lu	
Medical Device Link	http://www.devicelink. com	News; Consultants; Bookstore; Links; Discussion; Magazines (MDDI; MPMN; IVD Technology)

(*Continued*)

Organization or Publication	Web Address (Url)	Sample Main Topics
Medicines Control Agency (MCA)	http://www.opengov.uk/mcahome.htm	
Medical Matrix	http://www.medmatrix.org	
Medical Research Council	http://nimr.mcr.ac.uk/MRC/	
MEDLINE (free)	http://www.ncbi.nlm.nih.gov/PubMed or http://www.medmatrix.org/Spages/medline.asp	List of free sites
MEDLINE	http://www.medmatrix.org/SPAges/medline.asp or http://www.medsitenavigator.com/medline/medline.html	A metasite with full and changing MEDLINE search engines; List of free sites
Medscape	http://www.medscape.com	
Multilingual glossary of medical terms	http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html	
National Archives and Public Records Administration	http://www.access.gpo.gov/su_docs/aces/aces140.html	Code of Federal Regulations; Federal Register; Laws; U.S. Congress Information
National Institutes of Health (USA)	http://www.nih.gov	
National Library Network	www.toxnet.nlm.nih.gov	TOXNET: Toxicology Data Network, a cluster of databases on toxicology, hazardous chemicals, and related areas
National Toxicology Program	http://ntp-server.niehs.nih.gov/	
New Quality System (QS) Regulation	www.fda.gov/bbs/topics/ANSWERS/ANS00763.html	FDA Talk Paper Announcing the GMP Final Rule text
Organised Medical Network Information	http://www.omni.ac.uk	
Pharmaceutical and Medical Safety Bureau—Japan	http://www.mhlw.go.jp/english	
PharminfoNet	http://www.pharminfo.com or http://www.pharminfo.com/phrmlink.html	Independent assessment of therapeutics and advances in new drug development
Pharmweb	http://www.pharmweb.net	Information resource for pharmaceutical and health-related information
Quality of Life	http://www.glamm.com/ql/guide.htm	The choice of instrument
Quality of Life Assessment in Medicine	http://www.glamm.com/q1/ursl.htm	This contains hypertext with references to QoL measurements divided into (a) assessment tools, (b) reference organizations and groups, (c) diseases, symptoms and specific populations, (d) the top ten journals that publish articles of interest to QoL assessment in medicine, (e) methodology, (f) bibliographical research.
Regulatory Affairs Professionals Society (RAPS)	http://www.raps.org	Certificates; Resource Center; Publications; Chapters; Related Links; Contacting RAPS
Reuters Health Information Services	http://www.reuters health.com	
SCRIP: World Pharmaceutical News	http://www.pjbpubs.co.uk/scrip	

(*Continued*)

Organization or Publication	Web Address (Url)	Sample Main Topics
SNOMED	http://snomed.org	Systemized Nomenclature of Human and Veterinary Medicines
Swedish Medical Products Agency	http://www.mpa.Se	
U.S. Department of Agriculture (USDA)	http://www.usda.gov	
Food Safety	http://www.foodsafety.gov/	
USDA—FMS	http://www.fsa.usda.gov/pas/default.asp	
Farm Service Agency		
USDA—FSA	http://www.fns.usda.gov/fns/	
Food and Nutrition Service		
USDA—FSIS	http://www.usda.gov/fsis	
Food Safety and Inspection Service		
U.S. Department of Commerce	http://204.193.246.62	Bureau of Export Administration; International Trade Association; Patent & Trademark; National Institute of Standards and Technology
U.S. Pharmacopoeia	www.usp.org/prn	
University of Pittsburgh	www.pitt.edu	
World Health Organization	http://www.who.int	Governance; Health Topics; Information Sources; Reports; Director-General; About WHO; International Digest of Health; Legislation (http://www.who.int/pub/dig.html)
WHO Collaborating Centre for International Drug Monitoring	http://www.who.ch/ or http://www.who.pharmasoft.se	

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