

# The Safety Assessment Process—Setting the Scene: An FDA Perspective

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## Abstract

The process by which the US Food and Drug Administration (FDA) evaluates the safety/hazard potential of the products under its purview has evolved from a constellation of scientific research achievements in toxicology and related areas and a succession of historical events, some tragic, which encouraged dramatic changes in the oversight and regulation of foods, drugs, and cosmetics. The process is science based and has, over the years, achieved significant success in protecting human health. The authority by which the FDA provides pre- and postmarketing oversight of the products it regulates is established in the Federal Food, Drug, and Cosmetic Act, which has been amended extensively to broaden FDA's authority to include different products and product classes and to include oversight of safety and efficacy, greater stringency regarding reporting requirements, and enforcement processes. The structure of the agency, which comprises six regulatory components and a principal multidisciplinary research facility, is both practical and functional, providing regulatory oversight, regulatory guidance to industry, and fundamental and applied research. FDA's participation in different national and international scientific initiatives has helped bring focus to the prioritization, standardization, validation, and globalization of testing strategies and methodologies and the practical and widespread application of these initiatives to the regulation of consumer products. The agency is a leading advocate of alternative methods that refine procedures using animals to limit pain and distress, reduce and replace animal use in research and testing as scientifically appropriate and feasible, and have the potential to yield data comparable with or better than that obtained from conventional methods. The current scientific and technological advances and the rapidity with which they emerge offer new opportunities for the scientific community, industry, and regulatory authorities to alter current toxicological practices and promote the use of validated, reliable, and relevant alternative methods.

**Key Words:** FDA (Food and Drug Administration); Food, Drug, and Cosmetic Act; history; ICH (International Conference on Harmonization); regulation; safety and efficacy; toxicology

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## Introduction

Safety assessment, from the standpoint of the US Food and Drug Administration (FDA<sup>1</sup>) and the products it regulates, has evolved over time into a complex and extensive process using test methods that are relied on to help ensure public health. The history of regulatory safety assessment was substantially influenced by a series of human health hazards and tragedies that befell the US population as well as that of other countries. Public appreciation of such threats to their well-being had aroused widespread national distrust and uncertainty regarding the safety of foods, drugs, and environmental chemicals. It was clear that change was needed. This presentation includes a brief chronicle of events that have occurred over the last century and have resulted in some of the regulatory practices and testing conventions currently in place by which the FDA provides oversight for the products it regulates. Other details and milestones in US food and drug law history are available on the internet at <<http://www.fda.gov/opacom/backgrounders/miles.html>>, <<http://vm.cfsan.fda.gov/~lrd/history1.html>>, and <<http://www.cfsan.fda.gov/~lrd/history2.html>>. Information sources available in the published literature can be found at <<http://www.fda.gov/opacom/morechoices/sources.html>>.

## Regulation of Food, Drugs, and Cosmetics in the United States

The FDA is charged with protecting American consumers by enforcing the Federal Food, Drug, and Cosmetic Act (FDA 1997) and several related public health laws. Before 1906, there was no FDA as we know it today and there existed unrestricted sale of unsafe and unwholesome foods, unregulated sale and use of worthless, sometimes dangerous drugs and nostrums ("snake oils," quack medicines), and a

<sup>1</sup>Abbreviations used in this presentation: 3Rs, refinement, reduction, and replacement of animals used in research and testing; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health; CFSAN, Center for Food Safety and Applied Nutrition; CVM, Center for Veterinary Medicine; FDA, Food and Drug Administration; FD&C Act, Federal Food, Drug, and Cosmetic Act; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; NCTR, National Center for Toxicological Research; ORA, Office of Regulatory Affairs.

lack of safety and efficacy testing of such products marketed to the public. A turning point took place in 1906, when Upton Sinclair published his now famous book *The Jungle* (Sinclair 1906, 1981), which at the time was intended more as a statement of the deplorable working environment that existed in the Chicago stockyards than the more far-reaching exposé that it turned out to be. The book described the unsanitary meat packing practices and the general squalid labor conditions that prevailed. It revealed, among other things, that the contents of canned meat products were willfully and knowingly mislabeled, that putrid and septic meats were being sold to consumers, and that ground meats contained the remains of poisoned rats and body parts of plant workers who fell into their machines. These and other revelations led to an in-depth investigation of the meat packing industry by the federal government and the subsequent passage of pure food laws in the form of the 1906 Pure Food and Drug Act (FDA 1906a).

The federal Food and Drug Act of 1906, also referred to as the Wiley Act (after the Chief Chemist at the US Department of Agriculture at the time and “Father of the Pure Food and Drugs Act”), was the first legislation enacted for the purpose of “preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes” (FDA 1906b, 1934). This initial legislative action was, in effect, the most far-reaching directive of its kind and one that had no comparable antecedent that addressed human health and welfare issues as extensively. Yet, despite the seeming strength and dynamism of the pronouncement, the Act was weakened by the fact that the burden of proof to demonstrate whether products were contaminated, mislabeled, harmful, and so forth rested not with the manufacturer but instead with the government. The Act also established “official standards” of quality and purity and required that products meet only those standards. Still, there was no requirement for specific testing except for minimal animal studies to ensure physiological activity and perfunctory clinical studies to demonstrate that the drug “worked.” Furthermore, there was no requirement for premarketing approval, and the enforcement powers provided by the Act were limited, rendering its lawful enforcement arduous at best.

The inadequacies of the 1906 Pure Food and Drug Act (FDA 1981a) came to light with the sulphanilamide tragedy of 1938 (GMPI 2002; Linton 2000). Sulphanilamide was one of the first “sulpha” (sulphonamide) “wonder” drugs of the 1930s. Among its chemical properties, it was found to be highly insoluble in aqueous solvents but soluble in diethylene glycol. An “elixir of sulphanilamide” consisting of 10% sulphanilamide in diethylene glycol was made available for public consumption in 1937. The only factors taken into consideration before distribution were color, flavor, and odor; safety testing was not considered. The consequences of this inattention to safety considerations were 107 reported deaths, mostly children, and the death of the chemist

responsible for creating the formulation, who committed suicide.

The legislative response to this tragedy was the statutory issuance of the Federal Food, Drug, and Cosmetic Act (FD&C Act<sup>1</sup>) of 1938 (FDA 1981b). The FD&C Act provided FDA with new and more effective authority and, in contrast to its predecessor, the added lever of enforcement processes not previously available to encourage compliance. Noteworthy strengths and weaknesses of the Act related to oversight of drug manufacture are listed in Table 1. Of primary importance was that the Act required, for the first time, that a new drug be shown by the manufacturer to be safe within the dosage limits established by the manufacturer. This demonstration of safety was now required before marketing and to the satisfaction of FDA. The burden of proof of drug safety was shifted from the government to the manufacturer. The FD&C Act brought about the testing of drugs for toxicity to help define safe dose levels. It required the formal registration of manufacturers and allowed for factory inspections. Enforcement of these requirements was made easier by providing FDA with the authority to confiscate products that failed to meet the new requirements through seizure processes carried out by means of court injunctions.

Although demonstration of the safety of a drug became mandatory, the regulation of the efficacy of a drug was still not included under FDA’s authority. That authority was further constrained under the Act by FDA’s inability to take action against a drug previously available unless it could demonstrate proof of adulteration, contamination, or misbranding. Furthermore, the Act failed to provide for the requirement for submission of testing data to FDA before marketing authorization was granted.

Since its inception, the FD&C Act has been amended on several occasions for broader coverage and expansion of FDA authority. Notable amendments have included (1) the Durham-Humphrey Amendment of 1951, which added

**Table 1 Strengths and weaknesses of the Food, Drug, and Cosmetic Act of 1938**

Strengths	Weaknesses
Demonstration of safety required	Demonstration of drug efficacy not required
Toxicity testing required	Drugs marketed before implementation of the Act
Manufacturer responsible for proof of safety	not subject to its requirements
Manufacturer registration required	Premarket data submission requirements restricted
Manufacturing plants subject to inspection	
Seizures permitted	

FDA oversight of prescription drugs; (2) the Food Additives Amendment of 1958, which required that food additives must be demonstrated to be safe (i.e., not injurious to human or animal health); and (3) the Delaney Clause of 1958, which stipulated that any food additive found to be carcinogenic in laboratory animals or humans could not be added to the US food supply.

Drug-induced teratological disorders received significant attention and ignited strong public concern when yet another tragedy, the thalidomide tragedy (GMPI 2002), struck, primarily in Europe (circa 1960). Pregnant women's use of the tranquilizer thalidomide in Europe during a specific stage of organogenesis resulted in thousands of newborns with phocomelia deformities (i.e., a congenital absence of, or abnormal shortening of, arms and legs, often with only short flipper-like limbs projecting from the body). Prolonged and extensive evaluation of the safety of the drug delayed and ultimately prevented FDA authorization that would have permitted the drug to be marketed in the United States. Additionally, such reproductive anomalies were limited in the United States by exclusion of pregnant women from clinical trials, thereby precluding thalidomide-related abnormal births.

In 1962, Rachel Carson published her celebrated account of humans' chemical pollution of the environment, *Silent Spring* (Carson 1962). Her portrayal of the situation warned that in humans' war against pests that threaten the food supply, chemicals were being used that had the potential of creating greater problems than they were intended to solve. Her depiction called attention to the widespread and negligent use of synthetic pesticides, fungicides, and herbicides and forecasted the probable consequences of these practices in the form of contamination of rivers, streams, soils, crops, tissues of fish, birds, reptiles, wild animals and livestock, and humans themselves. Carson emphasized that, "For the first time in the history of the World every human being is now subjected to contact with dangerous chemicals from the moment of conception until death."

Although Carson's exposé addressed environmental concerns and apprehensions, it added to the collective governmental and public awareness of potential threats to human safety at a time of heightened sensitivity. This general appreciation of such health-related issues, compounded by the consequences of the thalidomide tragedy, confirmed the need to invoke sound measures that would pre-empt the indiscriminate and uninformed use of chemicals and drugs. One of the government's responses to these concerns was to amend the FD&C Act further with the 1962 Kefauver-Harris Amendment. The latter amendment required the submission of data on both the *safety and efficacy* of a drug for its intended use, and to the satisfaction of FDA, and required reporting such data *before obtaining authorization* to market a drug. Soon thereafter, FDA purview was further expanded in 1966 to include over-the-counter pharmaceuticals. A decade later, medical device amendments to the FD&C Act were enacted due to concerns over the availability of fraudulent and unsafe products and granted FDA

oversight and approval of medical devices. A chronicle of amendments to the FD&C Act from 1962 forward can be found in the *FDA Consumer* (FDA 1981c). The current FD&C Act is the one amended by the FDA Modernization Act of 1997. This version and its revised and new sections are on the internet at <<http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm>>.

The overall effect of these and related FDA regulations on industry was the progressive imposition of increasingly stringent preclearance requirements and postmarketing surveillance that mandated compliance with FDA standards for product quality, safety, and effectiveness. Indirect consequences of these federally imposed policies were that the extent of animal and human testing has increased dramatically and that product review times have lengthened from cursory to in-depth evaluations.

Additional resource information on FDA history (primary and secondary published sources and unpublished sources) is available from the US FDA *Guide to Resources on the History of the Food and Drug Administration, 2002* (<http://www.fda.gov/oc/history/resourceguide/sources.html>). The FDA also provides a website of its history at <<http://www.fda.gov/oc/history/default.htm>>. A comprehensive treatise on historical and current food and drug laws is available from the Food and Drug Law Institute (FDLI 2000).

## Organization of the FDA

To appreciate the obligations faced by industry and the extent of FDA oversight more fully, it is helpful to understand the organization of the agency (Table 2). FDA is composed of six regulatory components, of which five provide oversight of specific product areas. The product centers include the Center for Drug Evaluation and Research (CDER<sup>1</sup>), the Center for Biologics Evaluation and Research (CBER<sup>1</sup>), the Center for Devices and Radiological Health (CDRH<sup>1</sup>), the Center for Veterinary Medicine (CVM<sup>1</sup>), and the Center for Food Safety and Applied Nutrition (CFSAN<sup>1</sup>). An FDA website map that provides links to the different centers is

**Table 2 Organizational components of the US Food and Drug Administration (FDA)**

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Regulatory Unit
Office of Regulatory Affairs (ORA)
Product Centers
Center for Drug Evaluation & Research (CDER)
Center for Biologics Evaluation & Research (CBER)
Center for Devices & Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Center for Food Safety & Applied Nutrition (CFSAN)
Research Unit
National Center for Toxicological Research (NCTR)

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available on the internet at <<http://www.fda.gov/sitemap.html>>.

CDER ensures that brand name and generic prescription and over-the-counter drugs are safe and effective. CDER also ensures the integrity of advertising for prescription drugs and monitors the use of drug products for unforeseen risks to human health. Extensive information about CDER is available on the internet at <<http://www.fda.gov/cder>>.

CBER is responsible for the regulation of biological products including blood, vaccines, therapeutics, and related drugs and devices. CBER is charged with ensuring the safety of blood and blood products, the safety and effectiveness of childhood vaccines (including any future AIDS vaccines), oversight of human tissue for transplantation, allergenic materials and antitoxins, and the safety and efficacy of biological therapeutics (including biotechnology-derived products). Extensive information about CBER is available on the internet at <<http://www.fda.gov/cber>>.

CDRH is responsible for regulating medical devices and radiation-emitting products. According to the federal FD&C Act (Sec 201), a medical device is defined as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease.” According to the Code of Federal Regulations (<<http://www.access.gpo.gov/nara/cfr/index.html>>), 21 CFR Part 1000.15, radiation-emitting electronic products include such implements as microwave ovens, televisions, sunlamps, medical and baggage inspection x-ray machines, and laser products such as CD and DVD players, light shows, and bar code scanners. Extensive information about CDRH is available on the internet at <<http://www.fda.gov/cdrh>>.

CVM regulates the manufacture and distribution of animal drugs and feed additives (medicated feeds) given to food-producing animals, thereby ensuring that food derived from treated animals does not contain unsafe drug residues and is therefore safe for human consumption. The drugs and food additives made available for use by pet (companion) animals also fall within CVM’s purview. Extensive information about CVM is available on the internet at <<http://www.fda.gov/cvm>>.

CFSAN is responsible for ensuring that the nation’s food supply is safe, sanitary, wholesome, and truthfully labeled and that cosmetic products are safe and properly labeled. Some of the specific areas included within CFSAN’s purview are the safety of (1) substances intentionally or unintentionally added to food (including ionizing radiation, color additives, and indirect additives); (2) foods and ingredients derived by biotechnological means; (3) dietary supplements, infant formulas, and medical foods; and (4) cosmetic ingredients and products. Additionally, postmarket surveillance and compliance within the food industry are delegated to CFSAN. Extensive information about CFSAN is available on the internet at <<http://www.cfsan.fda.gov>>.

The other regulatory component of the agency is the Office of Regulatory Affairs (ORA<sup>1</sup>), which serves as the

primary office for all FDA field activities as they relate to field investigational and inspectional operations. Among ORA’s responsibilities are after-market oversight, ensuring compliance by regulated industry, and enforcement activities. Extensive information about ORA is available on the internet at <[http://www.fda.gov/ora/ora\\_home\\_page.html](http://www.fda.gov/ora/ora_home_page.html)>.

The primary research component of FDA is the National Center for Toxicological Research (NCTR<sup>1</sup>), which conducts peer-reviewed scientific research that supports and anticipates the FDA’s current and future regulatory needs. Those research efforts include fundamental and applied research designed to identify specific biomarkers of toxicity and to define biological mechanisms of action underlying the toxicity of products regulated by the FDA. The aim of the multidisciplinary research activities conducted by the NCTR is to achieve an understanding of the critical biological events in the expression of toxicity and to develop methods that would improve assessment of human exposure, susceptibility, and risk. In addition, the NCTR plays an essential role in the agency regulatory decision making process through its participation in the safety assessment of FDA-regulated materials and products. Extensive information about NCTR is available on the internet at <<http://www.fda.gov/nctr>>.

With these operational units in place, FDA is able to meet its overall responsibilities, which include (1) ensuring compliance with the federal FD&C Act and related regulations; (2) protecting and enhancing the public health through regulation of products under agency purview according to statutory authorities; and (3) ensuring availability of safe and effective products: foods, drugs, cosmetics, biologics, and medical devices. Within the FDA framework, each FDA center operates in accordance with different regulatory policies and procedures, such that a given center’s regulatory practices are dependent on the products within its regulatory sphere.

## International Conferences on Harmonization

Over the years, FDA has been engaged in a variety of scientific initiatives that have advanced the field of safety assessment and hazard prediction and have altered, even transformed, established toxicology practices. This paradigm shift has resulted in a change in the practical approaches used to assess toxicity and a change in the use of animal testing of FDA-regulated products. One such major effort, in which FDA was a primary participant and that occurred over the last decade, was the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH<sup>1</sup>). The ICH is the most recent and long-term effort aimed at internationally harmonizing the testing practices applied to pharmaceuticals.

Although not a primary objective of ICH, the resultant responsiveness to animal welfare issues that address the

refinement, reduction, and replacement of animal use in research and testing (3Rs<sup>1</sup>) has been an indirect consequence of the ICH harmonization effort. The regions involved in the ICH include Europe, Japan, and the United States. Both the regulatory and industrial sectors of each participating nation have representation, as shown in Figure 1. The aim of the ICH program has been to improve the efficiency in development and registration of new drugs with respect to safety and efficacy testing by providing consistency in worldwide regulatory assessments of drug products. This objective is being accomplished among the ICH participants by (1) eliminating the need for duplicative and inappropriate testing; (2) using harmonized requirements, methods, and data submission formats; (3) applying modified test procedures and testing regimens; (4) avoiding redundant tests that use animals; and (5) using scientifically justified alternative test methods where appropriate. Such harmonized reformation among the world's leading pharmaceutical manufacturing nations has begun to help bring about refinement, reduction, and replacement of animal usage.

Among the ICH preclinical safety testing guidances that affect the 3Rs are those for assessing carcinogenicity, genotoxicity, acute and chronic toxicity, and reproductive toxicity (Table 3). Additional details regarding the repercussions that some specific guidances have on the 3Rs are presented in Table 4. Overall, the ICH guidances touch upon all of the 3Rs as they apply to pharmaceutical safety testing. To this end, guidance is provided that permits the refinement of animal testing as it relates to minimizing pain and distress, the reduction of the number of animals used, and the replacement of animals with alternative nonanimal tests. Details regarding the various ICH guidances can be found on the internet at <http://www.ifpma.org/ich1.html> or at <http://www.fda.gov/cder/guidance/index.htm>, by selecting "ICH."



**Figure 1** Participants in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

**Table 3** ICH<sup>a</sup> preclinical safety guidances that affect the 3Rs<sup>a</sup>

ICH S1A/B: Carcinogenicity Testing of Pharmaceuticals ( <i>reduction</i> )
ICH S2B: A Standard Battery for Genotoxicity Testing of Pharmaceuticals ( <i>reduction, replacement</i> )
ICH S4A: Single Dose Acute Toxicity Testing for Pharmaceuticals ( <i>refinement, reduction</i> )
ICH S4B: Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent) ( <i>refinement, reduction</i> )
ICH S5A/B: Detection of Toxicity to Reproduction for Medicinal Products ( <i>refinement, reduction</i> )
ICH S6: Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals ( <i>reduction</i> )
ICH S7A: Safety Pharmacology Studies for Human Pharmaceuticals ( <i>reduction, replacement</i> )

<sup>a</sup>ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; 3Rs, refinement, reduction, and replacement of animals used in research and testing (italicized in body of table).

## The Changing Scene in Toxicology

Emerging science and new technologies are creating a metamorphosis in toxicological practices that will result in a significant transformation of regulatory toxicology over the next decade. Our accumulated knowledge and greater understanding of molecular biology and the molecular basis of genetic structure, function, and expression, plus the ongoing revolutionary scientific changes introduced by the new "-omic" technologies (genomics and proteomics) and other high-throughput technologies, will drive the evolution of toxicological practice and pharmaceutical development. Other scientific advances that offer additional opportunities for change include increased knowledge of cellular receptors, artificial intelligence and predictive modeling, noninvasive imaging technologies, transgenic and/or "humanized" animals, molecular biomarkers of toxicity, and bioinformatics (information technologies). Such advances are providing novel tools for industry's use in product development/drug discovery and improved early candidate selection. Advances of this kind also provide regulators with unique approaches for use in product evaluation and studying mechanisms of action. In the pharmaceutical arena, the resulting major increases in the number of new molecular entities and potential new and unique drug candidates will require new regulatory approaches and alternative regulatory strategies for assessing their safety and efficacy.

The impact of these advances offers promise for greater efficiency in animal testing, where such testing is necessary. Integrated approaches will permit combined efficacy/toxicity studies, integrated genetic toxicology assessments, and mechanistic carcinogenicity assessments, all of which will generate more data from fewer animals. Greater comprehension of nonclinical/clinical relationships and in vitro/

**Table 4 Aspects of some ICH<sup>a</sup> preclinical safety guidances consistent with the 3Rs<sup>a</sup>**

	Title	Guidance provided	Impact on 3Rs
S1A	The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals	Defines conditions for the conduct of carcinogenicity studies to avoid unnecessary use of animals	<i>Reduction</i> : Identifies situations when carcinogenicity studies may not be needed
S1B	Testing for Carcinogenicity of Pharmaceuticals	Approaches for evaluating the carcinogenic potential of pharmaceuticals	<i>Reduction</i> : (1) If primary study data clearly indicate a carcinogenic hazard, a second carcinogenicity study may not be necessary; (2) weight-of-evidence approach may be used; (3) use of scientifically justified alternative methods
S2B	A Standard Battery for Genotoxicity Testing of Pharmaceuticals	Recommends the standard battery of genotoxicity tests	<i>Reduction/Replacement</i> : Use of in vitro bacterial and mammalian cell tests; (2) an absence of systemic exposure in vivo supports use of only in vitro testing
S4B	Duration of Chronic Toxicity Testing in Animals	Time course for chronic toxicity testing in rodents and nonrodents	<i>Reduction/Refinement</i> : (1) Intended to help eliminate or reduce the need for duplicative (6- and 12-mo) animal testing; (2) use of chronic toxicity studies of shorter duration; (3) possible use of scientifically justified alternative approaches

<sup>a</sup>3Rs, refinement, reduction, and replacement of animals used in research and testing (italicized in body of table); ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

in vivo relationships will allow the use of shared, common biomarkers and other molecular attributes with which to monitor physiological responses in laboratory animals and humans. As those relationships are better understood and exploited, and more studies can be conducted in nonanimal systems or directly in humans, the need for animal studies will be reduced. The current dynamic technologies are providing the scientific field with opportunities previously unimagined. It is our responsibility to capitalize on those opportunities to secure the paradigm shift and promote the use of validated reliable and relevant alternative methods.

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Note: The reader is referred to the internet web addresses referenced in the text for supplemental information on the various topics covered.

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