Perspectives on Risk and Regulation
The FDA at 100
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Editors
Arthur Daemmrich
Joanna Radin

Chemical Heritage Foundation
Philadelphia, Pennsylvania
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Milestones in the History of U.S. Food and Drug Law

1862
President Abraham Lincoln appoints a chemist, Charles M. Wetherill, to serve in the new Department of Agriculture. This marks the beginning of the Bureau of Chemistry, predecessor of the U.S. Food and Drug Administration.

1883
Harvey W. Wiley becomes chief chemist, expanding the Bureau of Chemistry’s food adulteration studies. Campaigning for a federal law, Wiley is called the “Crusading Chemist” and “father of the Pure Food and Drugs Act.”

1898
Association of Official Agricultural Chemists (now AOAC International) establishes a Committee on Food Standards headed by Wiley. States begin incorporating these standards into their food statutes.

1902
The Biologics Control Act is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.
1906
The original Food and Drugs Act is passed by Congress on 30 June and signed into law by President Theodore Roosevelt. It prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs. The Meat Inspection Act is passed the same day.

1913
The Gould Amendment requires that food package contents be “plainly and conspicuously marked on the outside of the package in terms of weight, measure, or numerical count.”

1927
The Bureau of Chemistry is reorganized into two separate entities. Regulatory functions are located in the Food, Drug, and Insecticide Administration, and nonregulatory research is located in the Bureau of Chemistry and Soils.

1930
The name of the Food, Drug, and Insecticide Administration is shortened to Food and Drug Administration (FDA) under an agricultural appropriations act.

1938
The Federal Food, Drug, and Cosmetic Act of 1938 is passed by Congress, with provisions that require new drugs to be shown safe before marketing, that safe tolerances be set for unavoidable poisonous substances, and that the FDA inspect factories.
1940
The FDA is transferred from the Department of Agriculture to the Federal Security Agency, with Walter G. Campbell appointed as the first commissioner of food and drugs.

1945
The Penicillin Amendment requires FDA testing and certification of safety and effectiveness of all penicillin products. Later amendments extended this requirement to all antibiotics. In 1983 it was found that such control was no longer needed, and so it was abolished.

1949
The FDA publishes guidance to industry for the first time. This guidance, “Procedures for the Appraisal of the Toxicity of Chemicals in Food,” came to be known as the “black book.”

1951
The Durham-Humphrey Amendment defines the kinds of drugs that cannot be safely used without medical supervision and restricts their sale to prescription by a licensed practitioner.

1955
The Division of Biologics Control became an independent entity within the National Institutes of Health, after polio vaccine thought to have been inactivated is associated with about 260 cases of the disease.

1958
The Food Additives Amendment is enacted, requiring manufacturers of new food additives to establish safety. The Delaney proviso prohibits the approval of any food additive shown to induce cancer in humans or animals.
The FDA publishes in the *Federal Register* the first list of substances generally recognized as safe. The list contains nearly two hundred substances.

1960

The Color Additive Amendment is enacted, requiring manufacturers to establish the safety of color additives in foods, drugs, and cosmetics. The Delaney proviso prohibits the approval of any color additive shown to induce cancer in humans or animals.

The Federal Hazardous Substances Labeling Act requires prominent label warnings on hazardous household chemical products.

1962

The Kefauver-Harris Drug Amendments are passed to ensure drug efficacy and greater drug safety. For the first time drug manufacturers are required to prove to the FDA the effectiveness of their products before marketing them. The new law also exempts from the Delaney proviso animal drugs and animal feed additives that are shown to induce cancer but that leave no detectable levels of residue in the human food supply.

1966

The FDA contracts with the National Academy of Sciences–National Research Council to evaluate the effectiveness of four thousand drugs approved on the basis of safety alone between 1938 and 1962.

The Child Protection Act enlarges the scope of the Federal Hazardous Substances Labeling Act to ban hazardous toys and other articles.

The Fair Packaging and Labeling Act requires all consumer products in interstate commerce to be honestly and informatively labeled, with the FDA enforcing provisions on foods, drugs, cosmetics, and medical devices.
1970
The FDA requires the first patient package insert: oral contraceptives must contain information for the patient about specific risks and benefits.

The Environmental Protection Agency is established; it takes over the FDA program for setting pesticide tolerances.

1972
Regulation of biologics, including serums, vaccines, and blood products, is transferred from the National Institutes of Health to the FDA.

1976
The Medical Device Amendments are passed to ensure the safety and effectiveness of medical devices, including diagnostic products. The amendments require manufacturers to register with the FDA and follow quality control procedures. Some products must have premarket approval by the FDA; others must meet performance standards before marketing.

The Vitamins and Minerals Amendments (“Proxmire Amendments”) stop the FDA from establishing standards limiting potency of vitamins and minerals in food supplements or regulating them as drugs based solely on potency.

1981
The FDA and the Department of Health and Human Services revise regulations for human subject protections, based on the 1979 Belmont Report. The revised rules provide for wider representation on institutional review boards and detail what constitutes informed consent.
1983

The Orphan Drug Act is passed, enabling the FDA to promote research and marketing of drugs needed for treating rare diseases.

1984

The Drug Price Competition and Patent Term Restoration Act expedites the availability of less costly generic drugs by permitting the FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective. At the same time the brand-name companies can apply for up to five years of additional patent protection for the new medicines they developed to make up for time lost while their products were going through the FDA’s approval process.

1986

The Childhood Vaccine Act requires patient information on vaccines, gives the FDA authority to recall biologics, and authorizes civil penalties.

1987

Investigational drug regulations are revised to expand access to experimental drugs for patients with serious diseases with no alternative therapies.

1990

The Nutrition Labeling and Education Act requires all packaged foods to bear nutrition labeling. The food ingredient panel, serving sizes, and such terms as low fat and light are standardized.

The Safe Medical Devices Act is passed, requiring reporting to the FDA of incidents that suggest that a medical device probably caused or contributed to the death, serious illness, or serious injury of a pa-
tient. The act authorizes the FDA to order device product recalls and other actions.

1991

Regulations are published to accelerate the review of drugs for life-threatening diseases.

1992

The Prescription Drug User Fee Act requires drug and biologics manufacturers to pay fees for product applications and supplements and other services. The act also requires the FDA to use these funds to hire more reviewers to assess applications.

Nutrition facts and basic per-serving nutritional information are required on foods under the Nutrition Labeling and Education Act of 1990. The FDA and the Food Safety and Inspection Service of the Department of Agriculture redesign the food label to list the most important nutrients in a new format.

1993

A consolidation of several adverse reaction reporting systems is launched as MedWatch, designed for voluntary reporting of problems associated with medical products to be filed with the FDA by health professionals.

Revising a policy from 1977 that excluded women of childbearing potential from early drug studies, the FDA issues guidelines calling for improved assessments of medication responses as a function of gender. Companies are encouraged to include patients of both sexes in their investigations of drugs and to analyze any gender-specific phenomena.
1994

The Dietary Supplement Health and Education Act establishes specific labeling requirements, provides a regulatory framework, and authorizes the FDA to promulgate good manufacturing practice regulations for dietary supplements.

1997

The Food and Drug Administration Modernization Act reauthorizes the Prescription Drug User Fee Act of 1992 and includes measures to accelerate review of devices, regulate advertising of unapproved uses of approved drugs and devices, and regulate health claims for foods.

1998

The FDA promulgates the Pediatric Rule, a regulation that requires manufacturers of selected new and extant drug and biological products to conduct studies to assess their safety and efficacy in children.

2002

Under the Medical Device User Fee and Modernization Act the FDA can assess sponsor fees for the review of medical device applications, accredited third-party organizations may carry out device establishment inspections, and new safety requirements were established for reprocessed single-use devices.

The Office of Combination Products is formed within the Office of the Commissioner, as mandated under the Medical Device User Fee and Modernization Act, to oversee review of products that fall into multiple jurisdictions within the FDA.

2005

Formation of the Drug Safety Board is announced, consisting of FDA staff and representatives from the National Institutes of Health and
the Department of Veterans Affairs. The board’s mandate is to advise on drug-safety issues and work with the agency in communicating safety information to health professionals and patients.

2006

The FDA celebrates the centennial of the 1906 Federal Food and Drugs Act.
I.

Historical Perspectives
Chapter 1

Introduction

Historical and Contemporary Perspectives on the FDA

Arthur Daemmrich and Joanna Radin

Products regulated by the U.S. Food and Drug Administration (FDA) are ubiquitous in modern life and act as critical components of nutrition and health. The agency is responsible for the safety and effectiveness of prescription drugs, biologics, over-the-counter medicines, medical devices, cosmetics, nutritional supplements, and, with the exception of meat and poultry, all food products. Put in economic terms, the FDA regulates some 25 cents of every dollar spent by consumers; the total annual sales of products falling under the agency’s mandate exceed $1.5 trillion.

Currently, the FDA operates with a staff of approximately 9,100 employees and a budget of $1.5 billion. About one-third of the agency’s employees are stationed outside of the Washington, D.C., headquarters area, staffing over 150 field offices and laboratories, including 5 regional offices and 20 district offices. Investigators and inspectors visit more than 16,000 facilities a year, including an increasing number of manufacturing plants in other countries. The agency’s reach extends along the entire product development and testing pipeline for
new pharmaceuticals; its controls over medical devices, food, and other products are similarly extensive. The FDA has the federal authority to demand product recalls, halt production, and shape the language used to market many products. Decisions made about the safety and efficacy of new products can determine the viability of firms, especially in the pharmaceutical, biotech, and medical device industries.

Key turning points in the history of FDA regulation have often come in response to outcries over food- and drug-related tragedies. The high rate of new product introductions in modern biomedicine, processed foods, and nutritional supplements offers a compelling reason for FDA regulation above and beyond the historical specificities of its origins. In addition, these products have become essential to our lives: for example, recent studies have shown that over 40 percent of Americans regularly take a prescription medicine and 17 percent are on three or more medications. During the century since the passage of the 1906 Federal Food and Drugs Act the public has come to expect nearly absolute safety when consuming the products of science-based firms. To be uncertain about the contents of a jar of pickles, to find lead or radioactive materials in cosmetics, or to take a prescription drug with no active ingredients would be disruptive to daily life in a way that is inconceivable to most Americans. Such uncertainty would also pose an economic threat to an ever more tightly coupled economy in which many formerly disruptive illnesses have become rare and life span has extended from an average of 48.7 years in 1906 to over 77.5 years today. When the 1906 act was introduced, products with blatantly incorrect labels or containing inactive or dangerous ingredients were more common and consumers by necessity more cautious. In the century since, the interplay of science, innovation, commercialization, and regulation has fundamentally changed what we eat and how we receive medical care and has expanded the availability of other health and lifestyle choices.
Critical Contemporary Issues

Because of the widespread presence of many of the products under the FDA’s jurisdiction and their significance to our daily lives and long-term health, their regulation is highly contested. The FDA, industry, physicians and other professionals, and consumer groups are engaged in a complex set of negotiations concerning what counts as safety, efficacy, and health benefit. Consumers behave in ways not anticipated by scientists in government or industry. Regulation is costly, and compromises between absolute safety and market access are made daily. Only rarely is there complete agreement among the major players; more frequently, they find themselves at odds in any one of a variety of settings. Between intensive public media coverage, congressional scrutiny, and editorials in professional journals, FDA regulation regularly occupies the spotlight. This atmosphere of intensive oversight has been exacerbated by recent failure to retain senior personnel; the agency had a full commissioner for just sixteen months between 2001 and the end of 2006.

The FDA operates as a political and governing agency at the same time that it carries out a fundamentally scientific and medical mission. Its ability to govern is shaped strongly by the transparency of its processes and the representation of competing interests brought together in advisory committees and other forums for decision making. Simultaneously, employees are regularly called on to test products using sophisticated analytical instrumentation, evaluate complex biostatistical issues, and assess very intricate therapies and devices for an enormous range of ailments. The agency does not run clinical trials or directly test products, but to review results of tests carried out by companies requires a high level of scientific and medical expertise. With a strong commercial focus among firms seeking FDA approval, issues of conflict of interest, degree of training among reviewers, and length of decision time frequently come to the fore. More generally, given its
reach and mandate, it is inconceivable for the FDA to operate as a purely scientific institution with decisions emerging clearly from laboratory or clinical testing.

The industries the FDA regulates also face dilemmas concerning their core identities. They have recently oscillated between high esteem and complete dissatisfaction in public opinion, similar to the FDA. Members of the biomedical industry—pharmaceutical, biotechnology, and medical device firms in particular—operate on a complex boundary by, on the one hand, acting as free-market, for-profit firms and, on the other hand, providing a public service by inventing and delivering therapies that are vital for health and well-being. This boundary status is especially complicated for firms operating globally that have struck different compromises concerning product prices in different countries.

While rarely articulated on a national level, health and access to therapy are seen by many Americans as fundamental rights. In an era of unprecedented economic prosperity and scientific, technological, and medical progress, the prospect of narrowing access to care to matters of financial exchange and consumer purchase rightly troubles many people. Yet we and most authors in this volume would argue that the private sector offers an undeniably effective route to innovation and access. Advancing health care (including food, medicine, and lifestyle choices) as both a business and a public good is more than an interesting conceptual issue: it is the most significant pragmatic challenge facing our society. Given the history of failed initiatives to develop national health care, we suggest that the United States instead needs to develop a hybrid of private-sector firms and public-sector organizations focused on patients and consumers. Government, industry, and the broader nongovernmental-organization community will often be at odds. But we can and must do better at finding answers than we have in the recent past.
This volume is an effort to help foster communication and a greater spirit of collaboration among these separate institutions. No matter what solutions are found, the challenges we have outlined here will require the close involvement of the FDA with the pharmaceutical, medical device, food, and nutrition industries. Historical and contemporary perspective is critical to ensuring those solutions are reached efficiently and applied equitably.

About the Conference and This Volume

The chapters that follow were adapted from talks given by a remarkable set of speakers at a day-long conference hosted by CHF’s Center for Contemporary History and Policy and the Philadelphia district office of the FDA. The conference took place on 16 May 2006 and attracted over 250 attendees from the agency, regulated industries, academia, and the public. Using the occasion of the centennial of the 1906 Federal Food and Drugs Act, speakers reflected on the past while also exploring current and future issues in the regulation of drugs, medical devices, food, and nutritional supplements.

An atmosphere of collaboration, along with deep engagement with the challenges posed by the conference theme of “risk and regulation,” characterized the day’s events. Each of four main panels was composed of a representative from industry and a representative from the agency, facilitating a dynamic dialogue about the history, current state, and future of FDA regulation. These panels were complemented by two stimulating question-and-answer sessions, edited transcriptions of which are included here, and a closing plenary talk by Andrew C. von Eschenbach, the FDA commissioner.

This volume proceeds in four parts: part I introduces a set of historical perspectives on current issues on FDA regulation; part II looks in depth at drug and medical device regulation; part III brings the same level of focus to food and dietary supplements; and part IV concludes the volume with a chapter by von Eschenbach.
Laws regulating food and drugs have been found chiseled into stone tablets dating to ancient Sumeria. But as the FDA’s former chief counsel Peter Barton Hutt points out in his discussion of key legislative turning points in the history of the FDA, in the past hundred years consumers have seen truly significant impacts of government oversight on drugs, medical devices, food, and dietary supplements. Though the 1906 act, passed at the peak of the Progressive Era, represented an unprecedented effort to protect consumers and make industry accountable for its actions, it had certain inherent limitations. In chapter 2, Hutt documents how legislative and judicial actions taken before and since that time have shaped the agency’s ability to fulfill its mandate.

Challenges inherent in continuing to satisfy the mandate to protect public health and well-being, even as medicine becomes increasingly personalized, come to the fore in part II, which explores drug and medical device regulation. Each of the authors in chapters 3 through 6 engage with issues connected to the importance of public communication, postmarket monitoring of FDA-approved products, and the maintenance of agency leadership.

In chapter 3, Steven Galson, director of the FDA’s Center for Drug Evaluation and Research (CDER), posits that the agency’s continued success depends on its ability both to improve communication with the public and to cultivate a better understanding of how patients acquire information about drugs. After describing CDER’s efforts to improve its drug review process, refine its benefit-risk assessments of drugs, and manage increases in generic drug applications, Galson outlines specific strategies for enhancing drug safety and sharing advances in knowledge with the public in a timely and accessible manner.

Ronald Krall, senior vice president for worldwide development at GlaxoSmithKline, focuses on trends toward personalization in drug therapy in chapter 4. He considers how clinical research trials could be enhanced through greater alignment with the real-world experi-
ences and needs of physicians and patients. Krall envisions an increas-
ingly personalized, genomic medicine and an integrated drug surveil-
lance system that together contribute to improved patient diagnostics
and treatment. Echoing Galson, Krall calls for greater data sharing
and urges the FDA to explore more effective ways of communicating
its findings to both industry and physicians.

Turning to medical devices in chapter 5, Daniel Schultz, director
of the FDA’s Center for Devices and Radiological Health (CDRH),
focuses on the agency’s current activities, including the high-profile
Critical Path Initiative that seeks to develop the scientific infrastruc-
ture to bring innovative products to market more efficiently and expe-
diently. He identifies significant forces of change, including dramatic
increases in the complexity of medical devices, that are driving an
impending shift in regulatory strategies. The most notable of these
strategies is CDRH’s increased attention to monitoring the safety of
devices throughout their full product life cycle, including after they
have entered the market.

Robert O’Holla, in chapter 6, also considers the implications of
the introduction of devices of unprecedented complexity. In addition
to reflecting on changes in the regulatory environment over the thirty
years he has worked within the medical device industry, O’Holla—
now vice president of regulatory affairs for medical devices and diag-
nostic products at Johnson & Johnson—considers issues raised by the
introduction of new categories of products, such as combination de-
vices that necessitate the involvement of both drug and medical de-
vice regulators. He concludes that in an atmosphere of rapid innovation
and change, renewed agency-industry commitment to collaboration
will be essential to responding to public concerns about device safety.

In the discussion session captured in chapter 7, which ends part II,
attention is focused on specific concerns of safety, privacy, and stan-
dardization as they relate to greater reliance on genomic and proteomic
data in diagnostic and therapeutic decisions. Other issues addressed
include the role of expert advisory boards in FDA decision making and associated conflict-of-interest guidelines.

In part III authors reflect on the importance of informing and protecting consumers while maintaining global leadership in the regulation of food and dietary supplements. In particular, they raise important points about how to capture changes in scientific knowledge on food or supplement labels, as well as the challenge for regulators and industry to understand how consumers read and interpret nutritional information that is presented on labels.

Robert Brackett, director of the FDA Center for Food Safety and Applied Nutrition, outlines in chapter 8 the ways in which social and demographic changes, along with scientific and market developments, are influencing the kinds of food people eat and the forms in which they encounter those products. In addition to these changes the FDA faces unique challenges in maintaining a simultaneous focus on local and global issues of food safety and food security in the post–September 11 era.

In chapter 9, Idamarie Laquatra, the director of global nutrition for the H. J. Heinz Company, draws attention to contributions from the nutritional and behavioral sciences for the accessibility of food labels. She argues that the FDA must adapt existing labeling requirements to facilitate consumer choice. Similarly to Brackett, Laquatra acknowledges the importance of the FDA’s leadership position among regulatory agencies worldwide, especially in the area of food safety.

Chapter 10 turns to nutritional supplements with a contribution from Barbara Schneeman, director of the FDA Office of Nutritional Products, Labeling, and Dietary Supplements at the Center for Food Safety and Applied Nutrition. Schneeman provides a compelling overview of key moments in the history of public health as they relate to the regulation of dietary supplements. Through a focused explanation of the FDA’s current approach to evaluating qualified health claims, Schneeman highlights the agency’s ongoing efforts to define what
counts as a supplement and to assess the nature of claims made by manufacturers.

Steven Mister, the president and CEO of the Council for Responsible Nutrition, asserts in chapter 11 that as the dietary supplements industry continues to grow, its success hinges on guidance from the FDA. He balances Schneeman’s historical account of supplements with a perspective from industry, locating today’s manufacturers at a crossroads. The presence of “rogue” producers in the current market, he argues, threatens to undermine the legitimacy of companies who desire to comply with the law and who invest in new product development based on mainstream science and medicine.

Questions raised in the second question-and-answer session, found in chapter 12, reflect participants’ interest in gaining a better understanding of how individual centers within the FDA assess the effectiveness of the educational components of agency initiatives. Discussion of the FDA’s plans for executing future regulatory actions connected to food and dietary supplements also figures prominently.

The volume concludes with prescient comments from the FDA’s commissioner, Andrew C. von Eschenbach. He observes that the capabilities promised by advances in genomics and proteomics suggest that we are moving toward a health care system that will not only be personalized but will also be predictive, preemptive, and more participatory. For the agency to maintain its status as the gold standard in the twenty-first century, von Eschenbach argues, the FDA must keep pace with rapid and dramatic changes in science and society.

The FDA’s Second Century

As 2006, the centennial year of the 1906 Federal Food and Drugs Act, came to a close, many of the pressing and pragmatic issues raised in greater depth throughout the book played out in a very public way. Issues concerning food safety were underscored in early fall when spinach contaminated with a virulent strain of *Escherichia coli* bacteria
sickened over two hundred people across the country and led to three deaths. Interestingly, the FDA’s very longevity came under fire in some media accounts: for example, on the program Nightline an ABC voiceover stated, “The mad cow outbreak in Britain compelled Europeans to modernize their regulations while American food inspection policy is based on laws written a hundred years ago.” In November the FDA oversaw the voluntary recall of over 11 million bottles of a generic form of the drug acetaminophen, when metallic shards from processing equipment were found in some tablets. Less than a month later FDA leaders once again found themselves in the public eye when the agency’s decision to reapprove silicone breast implants drew both criticism and praise from various sectors of the public and industry. Capping an eventful year, the U.S. Senate confirmed von Eschenbach as FDA commissioner in December.

Thus within a four-month period issues ranging from bacterial infection of an agricultural crop, to maintenance of high-tech manufacturing equipment, to disputed risk assessment of implants, to the agency’s senior leadership kept the FDA in the limelight. In the same period FDA officers carried out thousands of inspections; made over 680 formal decisions concerning new drug approvals, labeling revisions, or expanded indications for drugs on the market; and performed myriad other “routine” activities. Contrary to some portrayals, this is not a government agency on the brink of collapse.

Nevertheless, the FDA faces significant issues as it moves into its second century of regulatory leadership. It will not be possible to maintain its reputation as the gold standard in health and safety nor its status as a leader in public health and regulation without learning from its rich history and taking a strategic view of where biomedicine and public health are headed in the future. We intend for this volume to continue fostering dialogue among the FDA, industry, academia, and, most important, the public. After all, there is no one among us—regardless of professional or personal affiliation—who is not inti-
mately affected by FDA decisions about what medicines, medical devices, foods, nutritional supplements, and other products are on the market.

**Endnotes**

3. This scrutiny is evidenced by over four hundred articles in the *New York Times* featuring discussion of FDA-related issues in 2006 and a nearly unbroken stream of congressional investigations since the early 1950s.
Regulation of food and drugs is the oldest recorded form of government oversight of private enterprise. It has existed literally in every recorded civilization. Ancient laws written on Sumerian clay tablets contain requirements for food and drugs that are present in substantially the same form in our laws today. From that perspective the 150 years that the FDA has existed and the 100 years since the passage of the Federal Food and Drugs Act of 1906 occupy a very small part of the entire history of government regulation of food and drugs. Yet in this past century more progress has been made in regulation of food and drugs than in the previous 6,000 years, primarily because of scientific advances in testing, monitoring, and ensuring safety. As I will argue, the history of food and drug law is really the history of science. As science progresses, it has allowed the FDA to move forward with new and better ways of implementing our food and drug laws.

This chapter focuses on ten specific turning points in the history of the FDA, each of which either illustrates a general principle or a specific moment in time of historic importance to the agency. Together these turning points cover the period between 1850 and the present and document the rise of the FDA and its complex relationship with industry and broader political forces in the United States.
The Origin of the FDA

The first turning point is the origin of the FDA as an institution. The significance of this event as a turning point becomes clear in the context of the history of science in the U.S. government. Federal interest in science originated with the Patent Office, which was created as the only science-oriented aspect of the Constitution. In 1837 the patent commissioner, Henry Ellsworth, made the first call for a national center for science to support the agricultural industry. Over the next thirty years his successors Edmund Burke, Thomas Ewbank, and Charles Mason repeatedly asked Congress to appropriate funds to support scientific investigations, particularly of the food industry. At that time very little distinction was made between food and drugs.

In 1850 Commissioner Ewbank established an Agriculture Division within the Patent Office, and somewhere between 1858 and 1860 the first analytical chemist was hired. That chemist was the first employee of what later would become the FDA. At the same time, the Agriculture Division set up a chemical laboratory to support that chemist. In 1862, when the Department of Agriculture was formed by Congress, a new entity was not actually created. Instead the Agriculture Division and its chemical laboratory simply were moved out of the Patent Office and designated as the new Department of Agriculture. That chemical laboratory was named the Chemical Division; the Bureau of Chemistry in 1902; the Food, Drug, and Insecticide Administration in 1927; and the Food and Drug Administration in 1930.

The First Requirement of Premarket Approval

The second turning point is the origin of premarket approval, which we take for granted today. Prior to 1900 no government had ever required that any article of commerce first be approved by the government before it could be marketed. All regulatory statutes before 1900—in all governments around the world—relied on postmarket policing.
They established principles to which industry was required to adhere and which were enforced as products were sold.

This situation changed at the turn of the last century. Because of two tragedies in 1901—one in St. Louis, Missouri, and the other in Camden, New Jersey—the Medical Society of the District of Columbia petitioned Congress to create a statute to regulate biological products. Thirteen children in St. Louis had died of tetanus owing to a contaminated supply of diphtheria antitoxin vaccine. In Camden more than a hundred cases of postvaccine tetanus were documented, including the deaths of nine children. In response Congress drafted a law for the District of Columbia that embodied for the first time in history the concept of premarket approval. As planned, the law would require that every manufacturer of a biological product sold in the District of Columbia be licensed by the government before the product could be marketed.

Then an extraordinary thing happened. Zachariah T. Sowers, a private physician in the District of Columbia, thought it was ridiculous to have this law apply only to the district. He felt it should apply to the entire nation, so he brought in four of his patients for a meeting. Not coincidentally, they were the vice president of the United States, the chairs of the House and Senate committees on the District of Columbia, and the speaker of the House of Representatives. Overnight the law was changed to apply to the entire country, without any hearings, without congressional debate, and without any explicit realization that the concept of premarket approval had been created.

The Federal Food and Drugs Act of 1906

The third turning point is the first nationwide statute regulating food and drugs—the Federal Food and Drugs Act of 1906. In 1879 E. R. Squibb gave a speech to the New York Medical Society calling for a nationwide food and drug law. Squibb felt industry needed a level
playing field. At that time the market was fraught with firms selling fraudulent products, making competition difficult for legitimate manufacturers. Ten days later the first bill for a national food and drug law was introduced in Congress. The predecessor of the U.S. Chamber of Commerce, then called the National Board of Trade, offered a thousand-dollar reward to the person who could draft the best national statute. Amazingly, the prize was won by a public analyst from England who plagiarized from the 1875 English food and drug law.

With a few minor changes this was the bill approved more than two decades later by Congress as the Federal Food and Drugs Act of 1906. Why did it take so long? The delay was not the result of opposition by industry or fights among government agencies. The Supreme Court at the time interpreted the concept of interstate commerce very narrowly. Under prevailing judicial decisions the states exercised sole control over the production and distribution of food and drugs, except at the moment when they were actually crossing state borders. Federal authority was limited largely to imported food and drugs. This state of affairs changed, however, when a dedicated socialist and muckraker, Upton Sinclair, published his novel *The Jungle*, which exposed the terrible conditions of the meatpacking industry. Reaction to the book compelled Congress to enact both the Federal Meat Inspection Act and the Federal Food and Drugs Act in 1906.

The 1906 act was a milestone in our nation’s history, representing an unprecedented federal effort to protect consumers. It changed the American food and drug supply forever. I believe it deserves far more recognition and credit than it currently receives.

**Affirmative Labeling Requirements**

The fourth turning point was the establishment of affirmative requirements for labeling of consumer products. The 1906 act had nothing in it that required what we regard today as “normal” labeling. There was
no affirmative requirement to put anything at all on the label. The act simply prohibited adulteration and misbranding. During a set of congressional hearings held in 1912, affirmative labeling emerged as a major concern. The following year Congress enacted the Gould Amendment to require that the net quantity of contents appear on every food package in clear form as required by regulations promulgated by the FDA. This was a landmark decision for the United States. Other countries had had affirmative labeling requirements in place for centuries. Bakers in ancient Rome, for example, had to write their name on each loaf of bread so that the consumer would know how to find the maker of a fraudulent loaf.

Since the 1913 Gould Amendment, Congress has added one labeling requirement after another. Today labeling is one of the major strategies by which the FDA implements our federal legislation.

The Federal Food, Drug, and Cosmetic Act of 1938

Turning point number five was the enactment of our current law, the Federal Food, Drug, and Cosmetic Act of 1938. In many ways the 1938 law was merely an expansion of the 1906 act. The new law maintained the basic concepts of prohibiting adulteration and misbranding but added cosmetics and medical devices to food and drugs as products subject to FDA jurisdiction.

The FDA first presented an argument for regulating cosmetics and medical devices during congressional hearings conducted in 1912, and it took from 1912 to 1938 for the FDA to obtain that legal authority. The 1938 act also bolstered affirmative labeling. No longer would consumers find just the net quantity of contents on the label. Now food manufacturers also had to provide their name and address as well as the name of the food and a statement of ingredients. Manufacturers of drugs faced the additional requirement of providing adequate directions for use. Americans take these requirements for granted today, but they are of relatively recent vintage.
Despite its success in extending the FDA’s jurisdiction, the 1938 act failed in some regards. It still contained no specific provision for premarket approval. As a result of the elixir of sulfanilamide disaster—where over a hundred people, mostly children, died in the fall of 1937 after taking an elixir that used diethylene glycol as a solvent—Congress added premarket notification for new drugs to the act. The 1938 act stopped short, however, of requiring premarket approval for all new drugs.

The 1938 act also failed to provide the FDA with jurisdiction over advertising. In the initial version of the 1938 law the FDA would have wrested control for the advertising of food, drugs, cosmetics, and medical devices from the Federal Trade Commission (FTC). The resulting disagreement over jurisdiction took five years to settle and was finally resolved with the enactment of two statutes: the Federal Food, Drug, and Cosmetic Act and the Wheeler-Lee Amendment to the Federal Trade Commission Act, which expanded the FTC’s mandate. Basically, the jurisdictions of the two agencies were kept the same: the FDA over labeling and the FTC over advertising.

Finally, I should point out that it is an anomaly to call the 1938 act our “current” law. In the past sixty-eight years it has been amended more than a hundred times. Even so, the basic elements of that law still stand and remain extraordinarily important to consumer protection.

**Strict Criminal Liability**

From the FDA’s origin enforcement has always been an important, if not the most important, priority. Under the 1906 act the FDA was created as a law enforcement agency. By the 1920s, for example, the FDA was bringing to court between five hundred and a thousand criminal prosecutions of companies per year. (Today there are fewer than five per year.) Also in the 1920s the FDA was bringing to court between two thousand and three thousand seizure actions. (The
current average is around twenty per year.) These legal actions created an enormous amount of work for a small agency with a minuscule budget and focused staff priorities and other resources on prosecutions and seizures.

Turning point number six relates to a Supreme Court decision in a landmark criminal case, *United States v. Dotterweich* [320 US 277 (1943)]. In 1943 the FDA brought a legal action against Joseph H. Dotterweich and the Dotterweich Pharmacal Company in Buffalo, New York, both of whom they charged with shipping adulterated and misbranded drugs across state lines. Although the company agreed to plead guilty if the charges were dropped against Dotterweich himself, the FDA refused, and the case ultimately went all the way to the Supreme Court on one critical issue. Dotterweich complained that he knew nothing about the violation. Legend has it that he was out of the country at the time the action occurred. He argued he had no criminal intent and no criminal knowledge, and therefore he should not be found guilty. The jury nonetheless found Dotterweich personally responsible, convicting him for the violations.

Affirming this decision, the Supreme Court laid down a principle that underlies all of food and drug law, underpins its enforcement activities, and is the key reason why industry is always anxious to comply with the law. The Supreme Court ruled that it was not necessary for the FDA to prove Dotterweich possessed criminal knowledge or intent. Because of the importance of food and drugs and the fact that they touch the lives of every citizen, the Supreme Court determined that any person who stands in a responsible relationship to a violation is guilty of a criminal act. I cannot overstate the importance of that decision. Other than the Meat Inspection Act—passed the same day as the 1906 Federal Food and Drugs Act—no other criminal law in American history up to the present day embodies the concept of what we call “strict criminal liability.” That is the reason why FDA enforce-
ment is taken so seriously, not just by the agency but by anyone subject to FDA jurisdiction.

The Transformation from Policing to Premarket Approval

The seventh turning point occurred in 1950, with the creation of the Keefe Committee. Before World War II the food supply consisted primarily of raw agricultural food. The challenge of feeding American troops distributed around the globe during the war required the nation’s food industry to change. Food technology advanced during those years in an unprecedented manner, and the use of preservatives and functional food ingredients proliferated. By the end of World War II the food supply had been completely transformed.

One member of Congress, Representative Frank B. Keefe of Wisconsin, concluded that Congress ought to investigate the use of chemicals in food. Yet Congressman Keefe suffered in two respects. First, he was from the opposition party. He was a Republican, and in 1950 the Democrats controlled the House and Senate. Second, he was quite ill and concerned about whether he would be able to live long enough to see the process through to conclusion. So he turned to his friend, Representative James Delaney (D-NY), and asked him to take up the cause. After Keefe died, Delaney spearheaded a lengthy investigation, and the committee ultimately issued several reports, each of which pointed out that, while there was no crisis, Congress should adopt a policy of premarket approval for items that go into the food supply.

From that single investigation there arose the following six statutes: the Miller Pesticide Amendments of 1954, the Food Additives Amendment of 1958, the Color Additive Amendments of 1960, the New Drug Amendments of 1962, the Animal Drug Amendments of 1968, and the Medical Device Amendments of 1976. All these took policing statutes and transformed them into premarket approval requirements. These statutes changed the basic architecture of the 1938
Chapter 2

act and also changed forever how the FDA would regulate the vast bulk of the industry.

Congressional Oversight

For the eighth turning point I offer the beginning of congressional interest in the FDA. In the period before the 1950s almost no congressional hearings focused on how the FDA was implementing the 1938 act or, before that, the 1906 act. The only hearings that were held examined very specific and narrow pieces of legislation. In 1958 one congressman, John Blatnick (D-MN), held a hearing on how the FDA was regulating the advertising for tranquilizer drugs, which at that point were just coming on the market in significant numbers.

The situation changed on 7 December 1959 when Senator Estes Kefauver (D-TN) unleashed an unprecedented attack on the FDA and the pharmaceutical industry in a series of what seemed to be never-ending legislative investigations and hearings that continued up until his death in August 1963. In hearing after hearing the industry was attacked as thoughtless and cruel. His three main concerns have equally strong resonance today: patents, prices, and profits.

With Kefauver’s death those hearings ended, but the precedent carried on, in part because in July 1962 the country first learned about the thalidomide tragedy, in which some ten thousand children were born worldwide with defects linked to the drug. Even though thalidomide was never permitted by the FDA to be marketed in the United States, Senator Hubert Humphrey (D-MN) and others immediately established a pattern of additional congressional investigations and hearings. As a result all who have served at the FDA subsequently have spent a lot of time testifying on Capitol Hill, and the FDA has received daily coverage by the news media. The FDA’s tenure as an obscure federal agency will never return.
User Fees

Turning point number nine relates to the advent of user fees. Before 1992 all FDA funds were appropriated through the federal budget, with two minor exceptions: the FDA obtained user fees from manufacturers for antibiotic certification and for the certification of color additives. But the amount of money involved was trivial. By 1990 it had become clear that Congress would no longer fund the FDA at a level anywhere near what the agency needed in order to do its job. Even industry realized that it no longer had a choice. The Prescription Drug User Fee Act (PDUFA) of 1992, followed by user fee laws for medical devices in 2002 and animal drugs in 2003, have set in place a system whereby industry pays the agency to review its applications. The FDA is currently developing plans for user fees for generic drugs and for food applications, and there have even been proposals to fund all enforcement activity through user fees.

We do not yet have sufficient historical distance to understand the ramifications of the introduction of user fees. While I do not know how such fees are going to change the FDA, I do believe the fear that they will somehow subvert the credibility of the regulatory process and the safety of drugs, medical devices, and other products is completely misplaced. Yet there is a limit to which the FDA's necessary regulatory activities can be funded with user fees. The FDA currently is being financially starved to death by Congress. The importance of what the FDA does as well as the importance of appropriating adequate resources for the agency to operate effectively must be made better known.

The First Amendment

The tenth and final turning point relates to the application of the First Amendment of the U.S. Constitution to the FDA. Before 1976
the First Amendment protection of free speech did not apply to commercial speech. In a landmark decision in 1976 [*Buckley v. Valeo*, 424 US 1 (1976)], the Supreme Court held that commercial speech was also subject to First Amendment protection. At that time, relying on the Dotterweich case, the FDA argued that the First Amendment did not apply to the agency because food and drugs were different than other consumer goods in that they touch the very lives of every citizen. That argument failed in 1999 with the landmark court decision of *Pearson v. Shalala* [164 F.3d 650 (D.C. Cir.1999)] where the U.S. Court of Appeals for the District of Columbia Circuit unanimously agreed that the FDA was subject to the First Amendment just like any other organization in the country.

If you look at the FDA conceptually, it only does two things. The agency regulates substances and it regulates words. The Court of Appeals decision—as well as the subsequent Supreme Court decision in *Thompson v. Western States Medical Center* [535 US 357 (2002)]—essentially told the FDA that half of what the agency had been doing was unconstitutional and the agency had to reform how it regulated labeling and advertising. We do not yet know the full ramifications of these decisions, but they obviously have had a major impact on the FDA.

**Conclusion**

I could have chosen a hundred turning points in the history of the FDA, but these ten present at least some of the important highlights. Looking back over the hundred years since the Federal Food and Drugs Act of 1906, it is evident that advances in science have driven regulatory action. It should also be evident that many of the protections we take for granted today can be traced to the 1906 act. At every turning point the FDA has been guided by concern for our health and well-being. We depend daily on the FDA to maintain the safety of our
food, drugs, medical devices, and cosmetics, but the future of the agency and of our health depends on our commitment to ensuring that the FDA has sufficient resources to fulfill its mandate.
II.

Drug and Medical Device Regulation
Ensuring the safety of drugs is a primary concern of the Center for Drug Evaluation and Research (CDER), and communicating effectively about safety, both within the agency and with stakeholders, is essential to fulfilling the FDA’s commitment to protect the public health. Seeking to achieve improved safety and communication goals, CDER is currently involved in a range of activities designed to strengthen the drug review process, critically assess current methods for determining benefits and risks, and manage increases in generic drug applications.

This chapter presents an overview of the kinds of activities that CDER is engaged in to attain these improvements. Among the most significant issues facing the FDA is the need to refine the agency’s approach to drug safety while ensuring that drug safety remains at the core of CDER’s commitment to the public health. I begin by outlining current initiatives dedicated to enhancing the safe use of drugs. Because issues of communication are closely connected to issues of safety, in the second part of the chapter I discuss new communication practices being implemented both within the agency and with
stakeholders. Improving communication includes developing better ways to assess and explain benefit-risk relationships. CDER faces challenges in adopting a more quantitative approach to benefit-risk assessment, which I describe in the third section of the chapter. Before concluding, I address current trends in generic drug applications and the issues they raise for the future.

Attaining excellence in the quality of and access to information about drugs is an effort CDER cannot accomplish on its own. One of the striking developments of recent decades is the extent to which the perspectives and interests of a diverse range of stakeholders, including members of the public, have become integral to FDA decisions about drug-safety communications.

**Drug Safety**

Results from a number of studies conducted by groups outside of the FDA will be essential in helping CDER improve drug safety. Recently, the center solicited a study through the National Academies’ Institute of Medicine to evaluate the existing drug-safety system. Findings from that study will help CDER streamline the ways it interprets and uses scientific data.

CDER is already implementing new safety assessment procedures. Some procedures reflect the findings of investigations of the center’s drug-safety practices initiated by Congress and the Health and Human Services’ inspector general during the past three years. Some of these procedures reflect the recommendations of a study on drug safety conducted by the Government Accountability Office. One challenge identified in the study was for CDER to improve the way disputes are resolved among those within the center who hold conflicting scientific opinions. The report also made recommendations for refining the scientific methods used for drug-safety assessment and decision making, particularly in the postmarket setting.
Issues connected to safety are perhaps most evident in the post-market realm. CDER is currently engaged in efforts to develop better techniques for detecting warning signals for drugs that are already on the market and improving how those signals are analyzed in the service of regulatory decision making. Establishing drug-safety surveillance contracts that integrate other parts of the National Health Information Infrastructure being created in the United States is related to this effort. These contracts have enabled the FDA to gain access to large, private-sector databases of information on outpatients’ exposure to medicines.

Furthermore, the FDA has established a new Drug Safety Oversight Board to provide independent oversight and advice on the management of important drug-safety issues. The board represents an innovative approach to drug safety. It comprises fifteen scientists, all appointed by the FDA’s acting commissioner, from offices throughout the FDA and other federal agencies. Not only will members track emerging safety issues and oversee their effective resolution, the diverse composition of the Drug Safety Oversight Board will also ensure that decisions about drug safety benefit from the input and perspective of experts both within and outside of the FDA. Additionally, the board will manage updates intended for health care professionals and patients about the benefits and risks of medicines as new information becomes available. Overall, the board has the potential to alter the benefit-risk analysis significantly for a drug and, in doing so, affect physicians’ decisions to prescribe the drug to certain patients.

Making sure CDER has the proper staff to implement and sustain these new programs will be critical to their success. With additional funding allocated by Congress, the center has begun to hire new staff with the appropriate expertise. CDER also recently appointed a new director of drug safety to lead the FDA’s postmarketing drug-safety program. We are confident that these latest actions will help CDER
successfully integrate the recommendations of its outside evaluators, leading to more effective decision making concerning postmarket drug-safety issues—issues that have been the focus of intense media scrutiny in recent years.

**Communication**

When the issue of drug safety began to attract significant media attention in 2004 during the controversy surrounding adverse events associated with COX-2 inhibitors, it became clear to those in CDER that one key challenge lay in communication: within the FDA, between the FDA and the public, and between pharmaceutical companies and the FDA. CDER is paying close attention to internal communication practices. The center is assessing how its staff members—specifically in the Office of New Drugs and the Office of Drug Safety—interact with each other and approach problem solving. The Office of New Drugs is responsible for approving new drugs and is involved in safety activities throughout the product life cycle, whereas the Office of Drug Safety focuses primarily on postmarket safety. Facilitating effective communication between these two offices will help expedite approvals and improve decision making about products already approved and on the market. To this end CDER recently published several guidance documents that explain the principles behind quality risk management for pharmaceuticals and provide examples of tools that support this effort. Such guidance should help FDA staff members as well as members of industry understand expectations surrounding risk management.

The importance of communication with the public about drug safety cannot be overstated. CDER has held Part XV hearings, as mandated by the Administrative Procedures Act, to give the public a voice in debates about risk communication and the direct-to-consumer promotion of drugs. Proceedings from these hearings will inform the formulation of CDER’s future drug-safety policies.
Hearing what consumers have to say, although essential, is not enough. CDER has also focused on developing new ways of communicating to the public. Recent controversies about selective serotonin reuptake inhibitors and such COX-2 inhibitors as Vioxx have already affected how CDER communicates risk information about approved drugs to the public.

The center staff understands that the public wants the FDA to share the information it generates as well as adverse event reports sent to the agency. Such concerns have been articulated in newspaper editorials, in medical journals, and by the medical community at large. A newfound activism is evident among medical journal editors, who have begun to refuse to publish articles about drugs unless the supporting data are made publicly available. For health care professionals to be able to make the best decisions for their patients, they must also have access to more of the information the FDA possesses.

At the FDA the power of the Internet is being harnessed to make information readily available to the public through a set of five initiatives. First, the amount of detailed clinical trial data posted to public data sources has increased dramatically. Much of these data are available at the National Institutes of Health Web site at www.clinicaltrials.gov. In a closely related effort CDER now develops health-care-professional and patient information sheets, which give consumers drug-safety information in an accessible one-page format.

Second, CDER is in the process of revising its proposed “Drug Watch” site based on public feedback. The drug-safety Web pages will continue to make emerging safety information available to the public in a timely manner and accessible format and will provide links to patient and health-care-professional information sheets.

The new Adverse Event Reporting System bulletin is a third effort to use advances in technology to communicate about safety. The system is a computerized database designed to support the FDA’s postmarket safety surveillance program for all approved drug and
therapeutic biological products. The data in this system will help the FDA when it takes regulatory actions to improve the public health, for example, when updating a product’s labeling information or re-evaluating an approval decision.

Fourth, the FDA has introduced a much improved drug label, which includes a “highlights” section with the most important prescribing information about benefits and risks. The highlights section also contains the date of the initial product approval and directions on how to report suspected adverse events for individual medicines.6

Advisory committees composed of outside experts have long provided the FDA with important insights regarding specific drug-safety issues. As part of a fifth initiative CDER is making available to the public via its Web site relevant materials from the proceedings of these meetings, including transcripts, briefing documents, and agendas.7

In addition to helping patients become more informed consumers of health care, the increase in data accessibility driven by these five actions will also benefit scientists who are asked to evaluate the medical validity of conclusions made by others about clinical trial data. For the FDA to remain a leader in the developing health information infrastructure, CDER must continue to take the public’s requests for information seriously and develop methods for providing better access to the data it possesses.

**Benefit-Risk Analysis**

Communicating with the public about drug safety involves transparency with regard to the agency’s approach to benefit-risk analysis. Currently, in addition to analyzing clinical trial data CDER staff often consults with members of expert advisory boards to reach an agreement on whether the risks of a given product outweigh the benefits. This approach has served the center well for several decades, but it involves a great deal of generalization and other methods are available for reaching decisions about benefit-risk. Certain quantitative meth-
ods used in other parts of our national public health and regulatory system, such as automobile or nuclear safety, may be applicable to pharmaceuticals. Even in the domain of food regulation, specifically in regard to pesticides, benefit-risk is much more quantitative than it is for drugs. Some of these methods may be useful in the drug review process to improve its quality and predictability.

Specifically, CDER is considering the potential applicability of techniques used to quantify risks, such as the “number needed to treat.” The number needed to treat is a meaningful way of expressing the benefit of an active treatment over a control and can be used either for summarizing the results of a therapeutic trial or for individualized medical decision making. One important outcome may be to adjust clinical trials as they proceed rather than having to wait until they are finished to evaluate the experimental therapy.

Applying the quality-adjusted life-year (QALY) concept to benefit-risk assessment for pharmaceuticals has also been suggested, although the United States does not appear to be inclined to adopt this approach. A QALY takes into account both quantity and quality of life associated with a health care intervention and evaluates them in economic terms. Essentially, the QALY provides a common currency for measuring the amount of health gain that would result from a given intervention. In some countries with national health systems, such as the United Kingdom, statistical controls and methods go so far as to shape decisions on drug access. However, a system in which each treatment option is evaluated from a purely economic perspective has significant limitations and is not likely to resolve ongoing debates about benefit-risk.

Indeed, even though certain quantitative methods may have the potential to improve the existing risk assessment process, they are not a panacea. Disagreements about CDER decisions will endure even if the center can attain perfect information and improve its analyses. The intractable nature of the conflict can be illustrated through the
example of isotretinoin, a highly effective drug for severe forms of acne that also carries a significant risk for birth defects if taken during pregnancy. There are some who argue that even one birth defect resulting from a drug used for a cosmetic purpose is intolerable. A restricted distribution program, iPLEDGE, which requires potential users of isotretinoin to demonstrate negative pregnancy, has been implemented to help reduce the risk for birth defects associated with its use.\textsuperscript{10} But regardless of how many improvements CDER makes, there will always be those who think that any degree of risk is unacceptable.

All interventions carry some form of countervailing risk. For example, a critical letter sent to the FDA from the American Psychiatric Association charged that by warning people about the dangers of selective serotonin reuptake inhibitors, the FDA is responsible for creating and promoting an increase in suicides in the United States.\textsuperscript{11} The authors claim that since the FDA issued its public health advisory warning about the risks associated with antidepressants, physicians have refrained from prescribing such medicines and patients are scared to take them.

The debate over benefit-risk assessment is further complicated by disagreements about whose responsibility it is to make such determinations. Should all the responsibility fall on the FDA and the government? Or should practitioners have more authority to make benefit-risk decisions for their patients? There is a strong perception among certain advocacy groups that, at a minimum, practitioners should be involved. Some patient groups even want that responsibility for themselves. They argue that patients should be able to make their own benefit-risk decisions. For example, certain terminally ill patients—as in the example of the case brought to court by the Abigail Alliance—want access to drugs that have only passed through the first phase of the approval process.\textsuperscript{12}

There are vitally important policy and constitutionally related components to risk debates, including arguments about how much
power the FDA has been given by Congress to make regulatory decisions in a range of areas, as well as disputes about the role of the states in regulating information about drugs and access to medicines. As states implement measures to allow their residents to obtain drugs from Canada and other parts of the world, these debates will continue and may even become more contentious.

Nevertheless, formalizing benefit-risk analyses and communication practices is an important FDA goal. Even though it is a contentious area, expanding the FDA’s role in communicating about the benefits and risks associated with the use of a drug is essential to the health and well-being of patients. Such issues are also directly relevant to the challenges posed by generic drugs.

**Generic Drugs**

Although little growth has occurred in many other parts of the agency in recent years, the number of generic drug applications reached over eight hundred in 2006, creating a considerable backlog in CDER’s application review process. Generic drug applications are simply outpacing the resources available for processing them (Figure 1).

This problem is serious because the efficient processing of generic drug applications has important implications for the public health, not least because the price of a generic drug is usually dramatically lower than its referenced brand-name drug. Once the patents on branded drugs run out, competition from generic producers becomes vital for the solvency of the Medicare program and payer organizations. Because the government is the nation’s largest consumer of health care through the Medicare and Medicaid programs, the rapid approval and processing of generic applications is essential to the continued health and financial stability of our federally sponsored health care system.

Although an estimated half of all prescriptions in the United States currently are filled with generic drugs, the FDA is working hard to communicate the viability and safety of generic drugs to help stem the
Figure 1. Generic drug applications, 1999–2005. A tentative approval is one for which all scientific and regulatory issues related to the application have been resolved, but because a patent or exclusivity is still in effect, the application cannot be fully approved. The work required of the FDA to issue a tentative approval is equivalent to that needed for a full approval.

To address the backlog in generic applications, CDER has taken a number of steps to enhance its review efficiency and throughput. It hopes, for example, that more efficient reviews can be achieved by improving early communication between generic drug companies and
the FDA, by hiring more review experts, and by giving industry guidance that will help applicants submit complete applications the first time around.

In addition to these efforts CDER is also considering the merits of requiring user fees for generic drugs. The user fees required by the 1992 Prescription Drug User Fee Act replaced the entirely government-funded drug review process with a system partially funded through fees paid by the pharmaceutical industry. These fees have given the FDA the ability to decide more quickly whether a new drug should be approved and have provided CDER with funds that are enabling it to upgrade its information technology resources. An analogous approach for generics might similarly speed review decisions without compromising safety.

**Conclusion**

Each of CDER’s offices and most of the center’s activities at least partially touch on ensuring the safe use of products in the marketplace. Although CDER spends close to 50 percent of its resources specifically on drug safety, fundamental progress in drug safety will only be made with continued investments in science and scientific processes—a key component of the FDA’s Critical Path Initiative. However, monumental strides in improving drug safety will not come until CDER has the capability to better predict which drugs will cause problems in which people and which people will benefit most, an issue discussed further by Ronald Krall in the next chapter.

In the wake of recent high-profile cases like those concerning the COX-2 inhibitors, some have argued that improvements in drug safety can be attained by separating the pre- and postmarketing functions at CDER and the FDA at large. But separating those functions is exactly contrary to what CDER needs to do. Closer integration of pre- and postmarket analysis will do more to protect consumers than will separating them. Pulling those groups apart would be a wasteful use of
taxpayer and other resources; it would further hinder the communication CDER knows is essential for success, and it would carry the center farther away from the very goal it is committed to achieving: making drugs safe for the people who use them.

Much as increased interaction and collaboration between the pre- and postmarketing functions of CDER will be essential to helping CDER achieve its potential, only through continued efforts to engage with experts and consumers alike can the FDA provide the kind of leadership that Americans have come to expect and other nations continue to admire.

Endnotes


2. The National Health Information Infrastructure (NHII) is a comprehensive and voluntary knowledge-based network of interoperable systems of clinical, public health, and personal health data that stands to improve decision making by improving accessibility to that information. For additional information see NHII, “FAQs about NHII,” aspe.hhs.gov/sp/NHII/FAQ.html (accessed 10 April 2007).


10. The FDA’s increased attention to protecting consumers from the potential side effects associated with isotretinoin, also known as Accutane, was publicized in a 12 August 2005 press release titled “FDA Announces Strengthened Risk Management Program to Enhance Safe Use of Isotretinoin (Accutane) for Treating Severe Acne,” www.fda.gov/bbs/topics/NEWS/2005/NEW01218.html (accessed 17 April 2007).


Chapter 4

Envisioning the Future of Pharmaceutical Regulation

Ronald Krall*

What is the future of pharmaceutical regulation? In this chapter I wind the clock ten years forward from the centennial of the 1906 Federal Food and Drugs Act and call for long-term and near-term changes that I believe will result in fundamentally improved medicines in 2016. From the 2016 vantage point I see at least two long-term changes with implications for pharmaceutical regulation: enhanced understanding about personal responses to medicines and the introduction of an active drug surveillance system.

Personalized Medicines

In 2016 the first thing I notice is that the new medicines being approved are described with information that is much more clinically meaningful to physicians and patients. Specifically, this prescribing information explains how individual patients will respond to the new therapeutic.

Table 1 shows an example of an adverse event section from the label of a medicine that is on the market today. This section of the

* The views presented in this chapter are those of the author and do not reflect official positions of GlaxoSmithKline.
drug label is very informative. It tells a physician that the drug was studied in comparison to a placebo and in a reasonably sized population of patients. Extrapolating from the placebo experience, it tells her or him that patients being treated for a major depressive disorder have many complaints. The label also indicates that specific adverse events, in this case sweating, nausea, and somnolence, appear more often in patients taking the drug than in those taking the placebo (see shaded rows in Table 1).

While a great deal of effort goes into capturing the data from which these tables and summaries are composed, we currently make poor use of those data. Today each adverse event is treated independently. Analyses are constructed to determine the proportion of patients who have each adverse event, but the relationship among adverse events is not analyzed.

What the label does not indicate, and what we do not currently determine, is whether any of the individuals who developed sweating also experienced nausea or whether any of the people who experienced nausea also experienced somnolence. We ignore the common clustering of adverse experiences that begin to describe phenotypes of patient response. But the challenges go even further than that. We also do not tell the physician—because we do not routinely assess it—when these adverse events occur or whether any of these patients got better. By neglecting to provide that kind of information, we fail to address some of the issues of greatest interest to the physician: do these adverse events occur together in the same patients or each in different patients? Do patients tolerate these symptoms, or do they find them intolerable and quit taking their medicines? When do the symptoms appear: right away or later in treatment? If they appear immediately, do patients develop tolerance to them, after which they disappear? Are there any things a physician or patient can do to moderate these symptoms? Are any of these symptoms harbingers of efficacy, or are
Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Trials for Major Depressive Disorder*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Paxil (n = 421) %</th>
<th>Placebo (n = 421) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a whole</td>
<td>Headache</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Sweating</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>4</td>
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<tr>
<td>Musculoskeletal</td>
<td>Myopathy</td>
<td>2</td>
<td>1</td>
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<tr>
<td></td>
<td>Myalgia</td>
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<td></td>
<td>Myasthenia</td>
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<tr>
<td></td>
<td>Paresthesia</td>
<td>4</td>
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</tr>
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</table>

* Physicians’ prescribing information; this table shows only a partial listing of the adverse experiences cited. Adapted from GlaxoSmithKline, us.gsk.com/products/assets/us_paxil.pdf (accessed 21 January 2007), with permission.
they seen only in patients who do not and will not respond to the drug and therefore signal that the physician should discontinue treatment?

One way to think about this problem is to conceptualize it in terms of a table (Figure 1) that has three categories of efficacy along the Y axis and four categories of adverse experience along the X axis. The individual figures in the table do not reflect actual patient counts but rather reflect the range of possible experiences that can result from a specific treatment.

Our clinical trial research would be more valuable if we identified those patients who fall into the specific categories defined by this table. For example, we should contrast those patients for whom the treatment is highly effective and without side effects (Figure 1, panel A) with patients who do not experience any efficacy and suffer intolerable adverse events (Figure 1, panel L). By classifying clinical trial subjects into these categories and then characterizing those subjects, we create the potential to predict who will benefit and who will not before patients are ever treated. From the clinical trial subjects who clearly experience efficacy but who also tolerate adverse events, we want to learn whether there are interventions that will ameliorate the adverse experiences, including lifestyle changes, different methods of drug delivery, dose adjustments, and the possibility of substituting the drug in question for a different member of the same class.

If pharmaceutical companies want to provide this kind of guidance in 2016, they must rethink the way in which clinical trials are conducted. Focusing solely on population effects, as trials do today, will no longer be satisfactory. As the move toward a more personalized approach to medicine continues, creating hypotheses based on phenotypic responses will be necessary. New analytical approaches for testing these hypotheses will also have to be adopted. Accurately characterizing these patients, however, will be more than a matter of phenotyping them. Genetic and protein profiling will certainly provide invaluable information, both as predictors and as markers of
individuals’ responses to drugs. The medicines of 2016 will surely include such markers in their prescribing information.

**Developing an Active Drug Surveillance System**

In 2016 not only is medicine more personalized, but drugs also are entering the market under a very different observational paradigm compared with today. In 2016 at least some and maybe all drugs are being released in ways that connect the knowledge learned through clinical research to the knowledge of how medicines perform in practice.

Today, when a new medicine is in development, between three thousand and five thousand patients are studied, at least a hundred of whom take the medicine for a year. Such studies are used to rule out

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**Figure 1.** Rubric for assessing the efficacy and adverse experience of a medication.
the probability of a serious adverse event occurring more frequently than in one in one thousand patients. In today’s world the effort to rule out a smaller risk is not considered worth delaying the potential benefits to patients.

However, within the existing regulatory paradigm, once a drug is approved and marketed, it rapidly exceeds the exposure it received during the clinical trial. Drugs that are prescribed in primary care settings for prevalent diseases can be expected to reach tens of thousands of patients in the first months following approval and perhaps a hundred thousand or more patients within the first year.

For the medicine whose label is shown in Table 1, such serious adverse events as hepatotoxicity that occur in as few as one patient in thirty thousand is cause for concern. The decision to withdraw a drug with a risk of that magnitude from the market has been made in similar situations in the past. Yet the shield of protection from the occurrence of this rare event is relatively thin. Often manufacturers and regulators do not have sufficient knowledge to modify the use of a drug with this level of risk, or withdraw it from the marketplace, until years after exposure to large patient populations has revealed the risk.

In essence, a significant limitation of the current approach to drug development is the necessity in registration trials to study a very small portion of the potential user population. When a new medicine is released to the entire population, we rely on spontaneous recording of adverse events to tell us whether the drug is behaving differently than predicted by or what is known from its registration trials.

The spontaneous adverse-event reporting system in the United States has been successful in recognizing serious adverse experiences. For example, a small number of reports of lactic acidosis, a potentially serious condition where the buildup of lactic acid in the body interferes with normal metabolic processes, appeared in the Adverse Events Reports System (AERS) database in the first five years of marketing of the HIV medication zidovudine. The cumulative number of
reports, along with published case reports, associating lactic acidosis with zidovudine led GlaxoSmithKline to modify its label for the drug in 1993. This action led to an increase in case reports in the same year, consistent with the well-recognized effect of publicity surrounding reports made to the AERS system.

In 2004 disproportionality analysis techniques, which employ Bayesian data-mining techniques that have become common in pharmacovigilance, were first applied to the AERS data. Figure 2 illustrates that the disproportionality analysis of these events detected that an excess of lactic acidosis adverse events for zidovudine actually occurred three years before it was recognized by traditional analyses.

The advent of disproportionality analyses of the AERS database has greatly improved signal detection. However, the system still falls short of the ideal because of reporting bias, lag time in detecting rare serious adverse events, the inability to calculate incidence rates, and our inability to detect modest increases in serious common adverse events of the kind seen with COX-2 inhibitors, such as myocardial ischemia.

By 2016, according to my predictions, the medical community will have found a better way to monitor the adverse events that occur with newly marketed medicines. By deploying electronic medical records widely throughout our health care system and drawing on new standards for the definition of medical data elements, a comprehensive surveillance system for medical events in the United States will have emerged. This system allows for monitoring of the effect of medical interventions by regularly (i.e., monthly or even weekly) assessing new or increased medical events that occur in the population of patients exposed to the intervention. Every new drug introduced into the health care system is actively monitored. No longer is marketing a drug a “let’s wait and see what happens” experience; instead it is a “let’s watch it as it happens” plan.
In 2016 this active surveillance system allows incidence of events to be assessed in a manner that is absolute, not probabilistic. It is 100 percent reliable in capturing events. The surveillance system allows the isolation of specific categories of patient profiles. It provides data about exactly how many patients have been diagnosed with the disease in question, how many were prescribed the drug in question, and how many continued to take the medicine and improved or recovered fully. In short, it provides tools for physicians to prescribe new medicines with greater confidence, knowing that there is feedback generating timely information about how best to use the medicine.

**Short-Term Imperatives to Achieving the Vision of 2016**

A number of shorter-term enhancements to pharmaceutical development and regulation are essential to achieving more effective medicines. First, in order to realize the benefits of the enhanced drug safety surveillance system described here, the FDA needs the authority to mandate changes in labeling after a drug has been approved. Following appropriate consultation, including with experts in the field and
with the company that manufactures the drug, the FDA must be able to issue updated labeling information.

Second, the FDA must develop a more effective way to communicate changes concerning prescribing information to doctors. As a chief medical officer I find myself caught between the rock of litigation and the hard place of the “Dear Health Care Provider” letters that inform physicians of changes to prescribing information. These letters are not the most effective way to communicate with physicians. Industry, physicians, and regulators must find a better way to share all of what we know about our products and our research.

Industry especially must also find a better way to manage communication of information about our products to physicians and patients in the many countries in which we operate around the world. Recently, we were forced to wait to communicate with American physicians in order to coordinate communication first with doctors in Europe. By waiting we achieved something rather extraordinary; completely coordinated communication in all the major countries of the world. But the delay inevitably kept information from physicians in the United States. This kind of choice is not one we can accept.

Industry, physicians, and regulators must develop ways of determining when a sample population studied in a single clinical trial can stand in for all the patients in the world and when it cannot. Because other countries are emerging as growing markets for pharmaceuticals and because those same countries are able to do very good clinical research, more discovery and clinical research will be done outside of the United States. Will research conducted using Chinese patients reveal what we need to know about American patients? Will the research be able to tell the Chinese what they need to know about themselves?

The pharmaceutical industry conducts great research to make medicines, but that is not what critics of the industry think. Pharmaceutical companies need to study the questions that those in the health
care system want answered. By 2016 the day of leaving those questions unanswered will be long gone. If the pharmaceutical industry does not figure out how to provide those answers, then I fear it will become the province of a U.S. equivalent of the U.K.’s National Institute for Health and Clinical Excellence (NICE), an independent non-governmental organization responsible for providing national guidance on the promotion of good health and the prevention and treatment of disease. For all its benefits NICE acts to ration drugs based on price, thereby restricting patients’ choices. The United States’ health care system is currently threatened by unacceptable costs, and leaders may ultimately be forced to make comparative decisions for Americans.

Today the United States dominates medicine internationally. The nation is not only a major consumer of modern medicines, the center for scientific research, and the center of clinical research. It is also the gold standard for drug regulation. Yet in a time of globalization other nations’ agencies may act faster, reach different decisions, or become more important on the global stage because of market changes and regulatory frameworks better adapted to the global marketplace. Acting on these near-term regulatory imperatives and achieving the longer-term changes I have predicted will keep the FDA at the forefront of worldwide regulation and will lead to the delivery of new, better described, and safer medicines.

Endnotes

Medical devices are critical to the delivery of health care in the United States. As defined by federal law, the term *medical device* encompasses nearly a hundred thousand individual products produced by more than fifteen thousand manufacturers. These devices range from such simple articles as tongue depressors and heating pads to such cutting-edge and complex devices as pacemakers, lasers, and imaging technologies.

In recent years the rate of change and complexity in medical devices has increased more sharply than at any other point in the last century. Future changes will be even more dramatic. How the FDA is handling the challenge of regulating medical devices in this atmosphere of rapid change and increasing complexity is the subject of this chapter.

Before describing several of the most significant issues driving the need for the Center for Devices and Radiological Health (CDRH) to augment its approach to regulating medical devices, I will discuss the framework that currently guides their regulation. In doing so, it is important to recognize that medical devices are distinguished from the other products under the FDA’s purview by the fact that they are regulated in accordance to their level of risk. In other words all devices are not subject to the same regulatory requirements.
One of the most significant areas in which CDRH has recognized the need to adapt is in ensuring the safety of medical devices in the postmarket realm. The center’s Postmarket Transformation Initiative is a comprehensive effort to augment its regulatory strategy to better identify, analyze, and act on information generated about devices after they have been introduced to the marketplace.

In addition to its efforts in the postmarket arena CDRH is also supporting improvements to its regulatory processes in the areas of staffing, information technology, risk communication, and public outreach, in part through the use of funds generated by user fees. I will discuss how the advent of user fees is facilitating such improvements to CDRH’s regulatory approach.

While ensuring the safety and effectiveness of medical devices is central to the responsibilities of the center, CDRH also maintains a long-standing commitment to managing the risks associated with radiation-emitting products. Before assuming its current title, CDRH was known as the Bureau of Radiological Health, and I will describe current activities in the domain of radiological health and point to resource issues that must be addressed to ensure that this important area of oversight is not compromised.

**Device Regulation Overview**

Although government authority to regulate therapeutic devices was first provided by the 1938 Federal Food, Drug, and Cosmetic Act, advances in medical technology soon made the law obsolete with regard to devices.\(^1\) Only with the passage of the 1976 Medical Device Amendments to the 1938 act was the FDA afforded specific authority to regulate the safety and effectiveness of such devices. The authors of the amendments recognized that devices are different than the other products the FDA monitors and, as such, stipulated that the regulation of individual devices should vary in accordance with their complexity.
Devices on the market at the time the amendments passed were assigned to one of three classes. Simple class I devices became subject to “general controls,” including quality system requirements for manufacturing; prohibitions against adulterated or misbranded devices; premarket notification requirements known as 510(k); the ability to ban device types; registration of manufacturing facilities; listing of device types; and provisions for record keeping, repair, replacement, and refund. Because class I devices are considered relatively low risk, a heavy-handed regulatory approach was seen as inappropriate.

Class II devices, which pose incrementally greater risk and whose safety and effectiveness cannot be controlled solely with class I requirements, became subject to “special controls,” which include guidance documents, patient registries, postmarket surveillance studies, and mandatory performance standards. Such devices normally reach the marketplace via the 510(k) premarket notification path discussed in more detail by Robert O’Holla in chapter 6. Premarket notification implies that a class II device must demonstrate substantial equivalence; it must be deemed at least as safe and effective as a device that is already on the market. Approximately 10 to 15 percent of class II devices must also undergo some form of clinical trial.

Class III devices, which usually are not only life sustaining but also the most complex and highest risk, must undergo the premarket approval process. This process requires an individual manufacturer to establish the safety and effectiveness of its product prior to marketing. For the majority of these devices, and especially for those that are permanently implanted in a human, extensive preclinical and clinical studies must be conducted, including animal and human testing.

Table 1 presents a rubric summarizing this approach to medical device regulation promulgated by the Medical Device Amendments and includes examples of devices in each class, as well as references, where applicable, to specific rules guiding regulation.
### Table 1. Medical Device Regulation by Class*

<table>
<thead>
<tr>
<th>Class/Relative Risk</th>
<th>Device Characteristics</th>
<th>Requirements</th>
<th>Device Examples</th>
</tr>
</thead>
</table>
| I: Low              | Simple; minimal potential for harm | Subject to “General Controls”:  
  - Domestic manufacturers, distributors, repackagers, and relabelers must register with the FDA  
  - A listing of device(s) to be marketed must be filed with the FDA  
  - Compliance with good manufacturing practices for devices†  
  - Devices must be labeled in accordance with regulations  
  - Submit a 510(k) prior to marketing device† | Elastic bandages, examination gloves, handheld surgical instruments |
| II: Medium          | More complicated than Class I devices, but not as critical as Class III devices | Subject to “General Controls” and “Special Controls”:  
  - May include labeling requirements, mandatory performance standards, and postmarket surveillance | Powered wheelchairs, infusion pumps, surgical drapes |
| III: High           | Support or sustain human life, substantial importance in preventing impairment of human health, or presents potential, unreasonable risk for illness/injury | Requires premarket approval (PMA) for devices:  
  - Regulated as new drugs prior to 28 May 1976 (transitional devices)  
  - Devices not found to be “substantially equivalent” to those marketed before 28 May 1976  
  - Pre-MDA devices that require a PMA application  
  - Devices introduced after 28 May 1976 that are substantially equivalent to those introduced before that date and for which the regulation has not been published in 21 CFR | Replacement heart valves, silicone gel-filled breast implants, implanted cerebella stimulators Implantable pacemaker pulse generators, endosseous implants |

* Additional details on rules for medical device classification can be found at U.S. Food and Drug Administration, Center for Devices and Radiological Health, “Classify Your Medical Device,” www.fda.gov/cdrh/devadvice/313.html.
† Most Class I devices are exempt from these requirements.
Forces of Change Driving the Shift in Regulatory Strategy

In the years since the framework for medical device regulation was implemented, medical device technology has moved forward with incredible speed. My expertise in what was then called “minimally invasive” surgery first brought me to CDRH in 1994. Since then attention has shifted from laparoscopy to miniaturization in the form of nanotechnology and the increased use of molecular and genetic markers for diagnostic purposes.

Not only do a significant number of new devices reflect advances in molecular science, many no longer fall solely under the jurisdiction of CDRH. In the last decade combination products, defined as “a product combined of two or more regulated components . . . that are physically, chemically, or otherwise combined or mixed as a single entity,” have presented a challenge to the existing regulatory paradigm.\(^2\) The polymer-based, drug-coated stent, which combines drugs with an existing medical device, is just one example of a combination product that requires the attention of both device and drug regulators. Combination products may also incorporate robotics or information technologies, further complicating regulation.

Although the FDA has established an Office of Combination Products to negotiate this uncertain terrain, many criticisms have been leveled at the agency’s approach to regulating these products. Manufacturers are concerned about issues related to the management of the review process when two (or more) FDA centers have review responsibility for a combination product, and consumers are worried about postmarket controls.

While the addition of new and exciting technologies to the market is desirable, keeping pace with innovation poses considerable challenges for regulators. The potential benefits of new products are often mitigated by the difficulty involved with identifying problems once the products reach the marketplace and effectively communicating about safety issues with the public. Devices are becoming both smaller
Regulating Medical Devices

and more complex. Implanted devices are being used for longer periods and in younger populations. At the same time, field resources for enforcing appropriate manufacturing and distribution are limited. All these factors underscore the importance of ensuring that CDRH’s regulatory strategy is appropriate for addressing rapid changes in device technology and dramatic shifts in the use of medical devices.

Clearly, the linear evaluation and communication approach of the past—where data first was collected and analyzed and conclusions were then made—is no longer effective. Information is being disseminated virtually as it is identified. Improving the ability to share information in a clear and timely manner with individuals possessing different levels of knowledge and experience is one of the FDA’s greatest challenges.

CDRH has already taken a significant step toward addressing these changes. Making improvements to the postmarket system for device evaluation will enhance patient safety as well as public confidence in the manufacture, review, and dissemination of both innovative and familiar medical devices.

Undertaking a Postmarket Transformation

As indicated by the overview of the FDA’s existing regulatory framework for devices, a significant amount of data is gathered during the premarket review process, particularly for high-risk devices. Nevertheless, for devices in each class no amount of premarket data can provide answers for all the questions that emerge in the postmarket realm. This is especially true for innovative devices.

In 2005 CDRH conducted a comprehensive inventory of its existing postmarket safety programs, looking at successes and challenges in implementing effective programs. The inventory evaluated not only how CDRH identifies postmarket problems and assesses the information obtained but also the response to that information through both stakeholder communication and enforcement action.
Through this inventory CDRH isolated several major factors that impede effective monitoring and assessment of the safety of already-marketed medical devices. While the center receives a large number of reports about adverse events, many more are not reported. Of the reports it does receive, information is often incomplete or vague, making it difficult to assess the source of the problem. Furthermore, in the world outside the lab, devices are often used in unintended and unanticipated “off-label” ways, making it difficult to discern whether an adverse event is inherent in the device or whether it resulted from inappropriate use. We are seeing a gradual shift from the use of devices in hospitals to private homes, which means more nonprofessionals are involved with using devices.

In light of these findings leaders at CDRH have devised a Postmarket Transformation Initiative to improve the FDA’s ability to ensure the safety of medical devices. The basic goals of the initiative are to assess accurate and timely data about adverse events, analyze this information quickly, and alert device users to potential problems.

Specifically, the initiative is focused on several key areas of improvement. The first involves developing a “culture of collaboration” on postmarket safety within CDRH that places more emphasis on networking to identify and solve problems. To accomplish this a senior-level team comprising center management and outside consultants experienced in medical device safety and product regulation has been appointed to guide the transformation process. The team will explore areas where external expertise might be applied to postmarket issues, including using preexisting advisory panels, working with medical and other professional societies to derive real-world data on device usage problems, and improving the dissemination of information.

CDRH must also develop world-class data sources and systems. The center aims to champion the development of a system to provide
unique device identification, a standardized and globally accepted nomenclature for devices, and mechanisms and incentives for device users to record this information in health care records. The center will also explore opportunities to partner with other groups to gain access to population-based health care data, as well as with practitioner, patient safety, public health, and industry groups in order to hone its ability to identify problems as they occur.

A third component of the initiative will involve maximizing CDRH’s ability to communicate information clearly and quickly to practitioners, patients, and consumers. The center will be assessing its existing communication tools and ensuring that staff understands how to deploy them effectively. When problems with devices are discovered, CDRH must improve the coordination, consistency, quality, and timeliness of inspections, reporting, and enforcement actions.

Facilitating Changes to the Regulatory Paradigm

The FDA’s Critical Path Initiative is now guiding our efforts to facilitate speedy approval of safe and effective devices and to ensure their safety and effectiveness in the postmarket realm. Critical Path was developed to address the fact that, while scientific knowledge is increasing, it is often not applied until the final stages of product development, which impedes public health benefits.

Priorities set through Critical Path are helping CDRH to focus its attention on identifying those aspects of device technology where better science would facilitate the regulatory process. One significant area of scientific development that may contribute to a more efficient review process is that of simulation. Computer models, such as the one currently referred to as the “virtual family,” will allow CDRH to implant virtual devices in virtual people. Working with simulated humans, center staff will be able to identify problems as well as potential benefits before a new device reaches patients. This technique will
facilitate the rapid movement of a given device through the approval process with minimal risk.

The Medical Device User Fee Modernization Act of 2002 has also played a substantial role in advancing CDRH’s efforts to change its existing regulatory paradigm. This act allowed CDRH to begin collecting user fees from companies that submit medical device applications, which has provided the center with an unprecedented source of resources resulting in tangible benefits to public health, including hiring new staff, strengthening the review process, reducing review times, and building a CDRH-wide culture that emphasizes improved coordination and accountability. User fees will continue to be critical in ensuring that the FDA is prepared to meet the challenges ahead.

Even as CDRH anticipates the reauthorization of the 2002 act, the advent of user fee programs has been accompanied by concerns about maintaining quality. To address these concerns the center has instituted a pilot program within the Office of Device Evaluation to assess its review process in terms of its component parts, which include biocompatibility, sterilization, packaging, and statistics.

Developing clear, well-framed expectations based on sound science is equally important to the review process. If CDRH’s guidelines are lucid, it is more likely that product submissions will not require revision, enabling the new technology to reach the market expeditiously. In pursuit of this goal CDRH is developing a focused and prioritized guidance program that involves conversation and collaboration with industry.

Maintaining quality of internal operations will also be important in facilitating change. Currently, 80 percent of CDRH’s resources are spent on payroll. CDRH must continue to employ the people appropriate for helping to meet regulatory challenges, and hiring new talent is not enough. Existing staff members need to stay abreast of innovations and breakthroughs in their respective fields. To help them CDRH is developing multiple programs within its staff college that encom-
pass technical training, professional and career development opportunities, and competency models in science, management, and business.

In an age of rapid scientific and medical progress CDRH must also strengthen its interactions with the academic and clinical communities. Special government employees and advisory panels already provide the center with critical support as well as a public forum for evaluating its products. In addition, CDRH’s medical device fellowship program continues to attract outside experts to work on a short-term basis; the center can tap into their expertise and gain critical external insights into its own policies and public health mission.4

None of these improvements will be sustained without the proper information technology. Currently, CDRH has several systems in place to track product submissions, including a device nomenclature management system; a “condition of approval” tracking system that allows the center to monitor postmarket studies; and E-Consult, a system that is dispersed over a wide geographical area facilitating communication throughout CDRH.

The “Turbo 510(k),” modeled on the electronic tax filing system, is intended to make the submissions and review process entirely electronic. It is being beta tested in the CDRH Office of In Vitro Diagnostic Device Evaluation and Safety. With the increasing number and complexity of submissions the premarket program operations modernization project will provide the center with a better means of archiving, tracking, and using all the information available. Another information management system under development is the electronic medical device reporting system, which will enable adverse event reports to be entered more quickly and at some point to use existing data-mining systems to evaluate those reports.

In the realm of outreach and communication CDRH’s top priority is to enhance the accessibility of its Web site so the public can get information in emergency situations and learn about medical device recalls. In order to make sure medical device safety messages reach
those who need them in a timely fashion, CDRH has made it a priority to cultivate an effective communications system that will link the center to clinicians, medical institutions, patients, and the general public.

The center’s E-Consumer Initiative is helping to foster dialogue with consumers, and in 2005 several new features were added to the CDRH Web site to offer users options for how they would like to receive information about medical devices and radiation-emitting products. New tools include an e-mail subscription service that alerts consumers when information of interest to them has been added or updated on the CDRH Web sites. It also allows users of the CDRH Web site to create profiles of interest by subject area. New RSS feeds even deliver up-to-the-minute medical device news directly to a user’s desktop.

Protecting Radiological Health

Although the percentage of radiation-emitting products in the new devices market has declined, they have fallen under CDRH’s jurisdiction since its creation. The FDA oversees radiation safety of imaging systems, counter-terrorism security systems (such as baggage and passenger screening systems for airline security), and industrial and electronic consumer products that emit radiation. For these products the FDA establishes performance standards and good manufacturing practices and conducts education activities to encourage safe use. Yet in the last thirty years the resources available for radiological health have been diminished, forcing a reconceptualization of the center’s responsibilities.

At this time one group in one location does all the work associated with radiological health. This group operates with the goal of aligning CDRH’s efforts with current and evolving public health needs and now is focused on ongoing problems associated with fluoroscopy. The
group is expanding its focus on patient, clinical, and consumer experience with radiation screening devices and suntan lamps. It is attempting to increase opportunities for information dissemination and training by partnering with professional associations and improving coordination across the radiological health community. In these efforts CDRH depends heavily on cooperation with states and other outside organizations.

The FDA’s 2005–2010 plan for the radiological health program will take into account worldwide performance standards, global markets for new products, and significant changes in the technologies of radiation-emitting products. The program will seek to maximize resources by focusing them on the products and procedures posing the highest risks to the public.5

Conclusion

I cannot overemphasize that all these efforts with regard to devices and radiological health are being enacted in an atmosphere of limited resources. CDRH is committed to making sure that every dollar spent, whether it comes from the public or from industry, is used efficiently. Moving forward, CDRH must manage effectively across the medical device product life cycle, promoting and protecting public health by ensuring the safety and effectiveness of medical devices and the safety of radiological products. The center must continue to ensure the health of the public even after a device has been approved, which means tracking devices from the development phase through the review process, to the postmarket phase, and all the way to their eventual obsolescence.

Although the world of medical devices is complex, it offers the promise of new and cutting-edge solutions to a number of our most vexing clinical problems. In coming years devices will change existing paradigms for the identification, evaluation, and treatment of disease.
They will also revolutionize the way treatments are administered. There is no question that medical device technology will fundamentally transform the health care system, as well as the way in which health care is delivered. Before those benefits can be realized, CDRH must further transform the way in which devices are regulated. Our health depends on it.

Endnotes


While 2006 marked the centennial of the 1906 Federal Food and Drugs Act, it was also the thirtieth anniversary of the addition of the 1976 Medical Device Amendments to the 1938 Federal Food, Drug, and Cosmetic Act. Signed into law by President Gerald Ford, the amendments sought, in his words, to “eliminate the deficiencies that accorded FDA ‘horse and buggy authority’ to deal with ‘laser age’ problems.” In the thirty or so years since the amendments’ implementation we have moved from the laser age to the information age. Throughout, I have witnessed firsthand the significant impact that such shifts in the FDA’s regulatory strategy have had on the medical device industry.

In this chapter I provide a decade-by-decade account of my experiences working with the FDA as a representative of the medical device industry. In this discussion of the interplay of the agency’s regulatory strategy, consumer engagement with health care, and industry-led medical device innovation, I highlight some of the major issues that have characterized the regulation of medical devices in the United States since the 1970s. Just as the way in which the FDA regulates
medical devices has changed, consumers’ awareness of and relationship to the regulatory process have also evolved.

After reviewing thirty years of milestones in medical device regulation history, I conclude by posing several open-ended questions about the future of medical device regulation. Looking to the past can often illuminate the present, and, with a clearer picture of the historical forces that have influenced regulation, it is also possible to speculate about the changes that lie ahead. Asking such questions today can help stimulate thinking and strategizing about how regulators and members of industry alike can most effectively approach the challenges we are beginning to encounter in the present and will have to confront and resolve in the future.

**Education and Cooperation: Device Regulation in the 1970s**

I began working in the medical device industry in the early 1970s, just prior to the passage of the amendments. At the time the decision to approve a medical device was generally made based on observational studies, which were much more common than the scientifically based controlled studies we are familiar with today. Physicians, many of whom sat on device review panels, relied on “art of medicine” evaluation techniques common to their own medical practices. The presence of these physicians on review boards accounts for the tendency of regulatory decisions to have a basis in clinical impressions about the safety of a given device rather than the FDA insisting on preclinical experimental data and controlled clinical studies.

In the late 1960s President Richard Nixon authorized investigations into device safety, which were underscored by several high-profile incidents involving medical devices in the early 1970s. In particular, the findings and media attention given to reports of failed cardiac pacemakers and injuries associated with the Dalkon Shield intrauterine device laid the groundwork for a dramatic change in the way devices were regulated. The timeliness of these tragedies, which
occurred during congressional hearings to assess the findings of Nixon’s 
Cooper Committee, helped spur the redefinition and categorization 
of medical devices that came with the passage of the amendments.

Before the 1976 amendments were passed, medical devices were 
defined within the Federal Food, Drug, and Cosmetic Act similarly to 
 drugs, as “instruments, apparatus, and contrivances, including their 
 components, parts, and accessories, intended for use in diagnosis, cure, 
mitigation, treatment, or prevention of diseases . . . or to affect the 
structure or any function of the body of man or other animals.” Most 
regulatory activity revolved around removing overtly fraudulent de-
 vices from the market. Yet under the 1938 law the FDA did not have 
the authority to require premarket approval of devices.

A significant aspect of the amendments was to create mutually 
exclusive regulatory categories for devices and drugs. The amend-
ments thus state that drugs cause a chemical reaction in the body, 
whereas devices do not. Furthermore, the amendments authorized 
premarket approval for certain devices and required all devices to be 
divided into one of three classes according to degree of risk, described 
in more detail by Daniel Schultz in chapter 5. This attempt to match 
the degree of regulation to the degree of risk associated with a device 
was one of the Medical Device Amendments’ most notable features. 
While the law greatly strengthened the FDA’s authority to regulate 
medical devices, it also required that regulation be carefully tailored to 
the type of device involved.

In classifying devices the amendments distinguished between those 
already on the market prior to its passage and new devices. New de-
 vices were immediately subject to premarket clearance requirements. 
The amendments also represented an expansion of the FDA’s author-
ity, granting the agency jurisdiction over manufacturers’ obligations 
for notification, repair, replacement, and refund of defective devices. 
The agency was also authorized to ban any device that presented a 
substantial or unreasonable risk for injury or illness.
Chapter 6

The first premarket notification submission I made to the FDA in the mid-1970s—known as a 510(k) and named for the section of the Federal Food, Drug, and Cosmetics Act that required it—came during the period before such procedures were mandated by the Medical Device Amendments. While the 510(k) regulation was being formulated, the FDA was accepting such applications on a voluntary basis pending the promulgation of the final regulation. A medical device manufacturer is now required to submit a 510(k) before selling a new device for the first time or before reintroducing a device that has been significantly modified such that its safety or effectiveness has changed. By today’s standards the paperwork required in the mid-1970s for a submission was minimal and in the case of my first 510(k) included a hand-drawn sketch of the device in question. The device was cleared by the FDA in two weeks. Clearly, the regulation of medical devices was in its infancy in this era.

In the 1970s the authorization of premarket approval applications took slightly longer than that of the 510(k), but unlike today the process was relatively uncomplicated. These applications are the most stringent type of device marketing application required by the FDA. They represent the agency’s process of scientific and regulatory review to evaluate the safety and effectiveness of class III devices, which are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk for injury. Approval of an application is based on a determination by the FDA that the submission contains sufficient, valid scientific evidence to ensure that the device is safe and effective for its intended use. An approved application is in effect a private license granting the applicant permission to market the device.

In the years immediately following the implementation of the amendments the Bureau of Medical Devices, now known as the Center for Devices and Radiological Health (CDRH), was guided by a
commitment to education and cooperation. Enforcement actions were reserved for only the most severe and recalcitrant offenders. The agency was interested in cooperating with industry to ensure the success of the new regulations and felt that educating noncompliant members was a more effective strategy than punishment. The FDA’s approach to regulating medical devices was new, and industry and government were learning together in an atmosphere of relative cooperation.

Not only was the regulatory environment of the 1970s different than that of today; consumer engagement with the regulatory process was also rare. Patients in the 1970s rarely questioned the recommendations or orders given to them by their physicians. They did not suggest or request one type of test or treatment over another. The public of that era was not as knowledgeable or critical of health care as they are today, and therefore they were rarely a visible presence in debates over the agency’s approach to regulating devices.

The public’s acceptance of decision making about medical devices, along with the cooperative regulatory environment, facilitated the approval of new devices; in the 1970s the process of approving a device and getting it to market was not greatly fraught with uncertainty or controversy.

**Complexity and Compliance: Device Regulation in the 1980s**

Medical technology changed dramatically in the beginning of the following decade. Although medical devices are continuously becoming more complex, the increase in the sophistication of devices in the 1980s was staggering. Not surprisingly, hand drawings in 510(k) submissions were no longer adequate, nor were they acceptable. In response to changes in devices themselves the FDA began to hire nonengineering staff; in turn these new reviewers had substantial implications for device review criteria.

With the restructuring and increased formality of medical device regulation following passage of the amendments, changes in data
requirements were inevitable, especially when viewed from today’s vantage point. Yet even as these new and more stringent data requirements were introduced, the large majority of 510(k)s and premarket approval applications were cleared in a reasonable period.

Inspections became more common in the 1980s, and the attention that had been devoted to education in the previous decade began to shift toward compliance and enforcement. Clinical studies gradually increased in complexity, and review panels began to pay more attention to the data they produced. The amount of time to approval for medical device submissions soon started to creep upward.

Toward the end of the decade Congress again became involved with device regulation, holding numerous hearings during which the FDA’s strategy for implementing the amendments came under attack. The hearings used several high-profile examples of devices whose risks had not, in the opinion of the members of Congress, been managed appropriately by the FDA. Some of the device examples used in the hearings included heart valves, pacemaker leads, and temporomandibular joint dysfunction devices used in scanning procedures. The FDA reacted to these charges by using even more precaution in its approvals. An unintended consequence of Congress’s criticism was that the device approval process became less predictable. In turn, the importance of regulatory professionals to industry increased, especially their ability to predict what review panels might require.

Congressional hearings into the situation led to passage of the Safe Medical Devices Act of 1990, which encompassed important changes to the Medical Device Amendments. The new act created substantially more postmarket authority for CDRH to regulate devices than existed even for drugs. The 1990 act also introduced the concepts of user reporting, removals and corrections, mandatory recalls, temporary suspensions of premarket approval applications, device tracking, postmarket surveillance, quality systems, design controls,
special controls, and civil money penalties. These changes to the agency’s authority provided CDRH with significantly more tools for enforcement, which were put into use over the course of the next decade.

**An Era of Enforcement: Device Regulation in the 1990s**

In the early 1990s, with the appointment of David Kessler as the FDA commissioner, the agency focused more directly on enforcement and then tightened clinical trial requirements, which directly affected the U.S. health care system. When Kessler ordered the seizure and destruction of a shipment of Procter & Gamble orange juice concentrate under the auspices that it was misleadingly labeled as “fresh,” he sent a message to industry that the FDA was entering an era where enforcement would be taken very seriously.

At the same time leaders at the FDA’s Center for Drug Evaluation and Research began to turn a critical eye toward CDRH’s review processes, particularly with regard to premarket approval applications. In 1993 a report led by Robert Temple, then director of the Office of Drug Evaluation, criticized the medical device review process for its lack of science-based evidence, concluding specifically that CDRH was not requiring adequately controlled clinical trials for premarket approval applications. In response, the FDA pressured CDRH to increase its attention to scientific data and compliance issues. Unfortunately for industry the agency neglected to define what this would mean in practice. As a result both CDRH review and field staff were left to negotiate what constituted adequate scientific evidence and how to determine what compliance meant both for themselves and for the industry.

Device review times soared. In 1994, 510(k) review times averaged 216 days. Approval of a premarket application took, on average, 823 days. A palpable sense of uncertainty about where the review
process was heading pervaded both industry and the FDA. Owing to growing media interest in FDA affairs, the public witnessed this confusion. Mistrust of the medical devices industry began to affect the overall health care system by slowing the introduction of new diagnostic and therapeutic instruments.

**Regulation in the New Millennium**

As the new millennium began, internal restructuring and a focus on speedier review by CDRH returned device reviews to a more reasonable time frame. By 2004 review of 510(k)s hovered around a hundred days on average, and premarket application approval times had been cut in half, to an average of 436 days.

Despite these improvements we currently face a range of unique and unanticipated challenges that complicate the review process. Most notably, firms are developing innovative combination products that are both drug and device. Even though the Safe Medical Devices Act includes criteria for the FDA to use in determining which center will regulate products that are combinations of devices and drugs, the FDA centers for drugs and devices must figure out how to overlay their regulatory requirements when industry presents them with such a product. For example, Johnson & Johnson has made significant advances in the development of stents that include both drug and device components. Our experience thus far indicates that the challenges presented by combination devices, which represent the future of the device industry, require further, focused attention.9

Another significant change under way is the rise in prominence of scientifically derived data. Unlike thirty years ago, physicians today are relying much more on large data sets than on the “art of medicine.” Not unexpectedly, this trend has affected what advisory panel reviewers look for when evaluating a medical device submission. Reviewers today are much less interested in the experience of using a device and much more interested in what the hard data says. As a
result clinical studies have become more complex and expensive than ever before.

With the public’s reaction to issues like those surrounding implantable cardioverter defibrillators—recently connected to two deaths and involving the recall of over seventy thousand devices worldwide—postmarket issues have risen to prominence.\textsuperscript{10} It was, in part, problems with similar devices that spurred the passage of the Medical Device Amendments in 1976.

Today, as a result of access to the Internet and the increased coverage of FDA activities by the popular press, the public is highly knowledgeable about the regulatory process and demands greater accountability from government and industry than in the past. The media feeds the public thirst for knowledge and has watered the seedlings of mistrust that were planted in the 1990s, fostering a public expectation of zero risk. That expectation is impossible to meet, and regulators and the industry must communicate more effectively with the public. It is important to recognize that the public’s concerns about the safety of devices are directed just as often at the FDA as they are at industry. We in industry share the challenge of presenting this risk equation at a level that the public can accept. While we wrestle with these issues currently, we must also begin to anticipate what the future holds for medical devices so that the public, industry, and the FDA can engage in a productive dialogue.

\textbf{Looking toward the Future}

I recently learned of a hospital that changes its practice guidelines every night as a result of what has been learned during the previous day. The hospital has invested significant resources in its health information technology system and has over three hundred people regularly updating a database with patient outcomes. These staff members also search the medical literature and input results into databases that allow them to adjust practice guidelines daily. When a physician
prescribes a drug or other therapeutic intervention and something noteworthy occurs—even just the previous day—all hospital staff members will learn of it on their handheld computer.

In such an environment what is the role of the regulator or even the manufacturer? How meaningful is the label on a device when real-time data is going to drive where and when a device will be used? In the future how meaningful will the term *off-label* (which refers to a physician using professional discretion to apply a device in a way not specified by the FDA-approved label) be in an environment of constant monitoring and data collection? How can a company make informed investment choices when getting approval is no longer very meaningful, when even approved products are denied adequate reimbursement, and when still more data is perpetually required?

Until recently regulation of medical devices worked in a fairly linear manner, perhaps best characterized as a “toll booth” approval system. Manufacturers gathered data, presented analyses to regulators, and then, it was hoped, got market approval. Industry’s focus has always been on understanding the predictability of the review process, that is, what is required and how fast a submission can be reviewed. With the revolution that has already begun in the quality and the amount of information available on a daily basis—information that drives how health care is delivered—will our definitions of predictability remain the same? As health information technology becomes more and more an integral part of health care delivery, will the “toll booth” approval system remain relevant?

It is not currently possible to provide answers to many of these questions, but they do suggest that regulators and industry representatives need to begin to rethink what regulatory system is most appropriate for the emerging information age. The time has come to develop a new paradigm, one that regulatory professionals in both government and industry have a hand in shaping.
While the nature of industry’s relationship with the FDA has shifted many times over the past thirty years, members of industry share the FDA’s commitment to navigating the challenges presented by the innovative devices we will be seeing in the decades to come. Developing a regulatory framework that can support the devices of the future will be an enormous undertaking. Yet it will not be possible for consumers to reap the health benefits of these devices with full confidence in their safety unless industry and agency renew the commitment to collaboration they have shared in the past.

Endnotes

2. Theodore Cooper, MD, then director of the National Heart and Lung Institute (now the National Heart, Lung, and Blood Institute), led the committee that surveyed medical journals and found evidence that during the previous decade medical devices had been associated with some 10,000 injuries, about 8,000 of them involving intrauterine devices; 512 deaths involving heart valves; and 89 deaths from pacemakers (Cooper Committee, Medical Devices: A Legislative Plan [Washington, DC: Department of Health, Education, and Welfare, 1970]).
4. Ibid.
5. Good manufacturing practice regulations to ensure that devices are manufactured to be safe and effective through quality design, manufacture, labeling, testing, storage, and distribution were also authorized by the Medical Device Amendments and issued by the FDA in 1978.

10. Implanted cardioverter defibrillators (ICDs) are surgically implanted medical devices used to shock the heart into a normal rhythm after patients suffer certain rapid life-threatening arrhythmias. In 2004 the FDA announced the voluntary recall of two older models of ICDs after the manufacturer Medtronic became aware of one serious injury and four deaths that may have been related to failure of the device. The following year Guidant recalled over seventy thousand of its cardiac resynchronization ICDs, one of the largest such industry regulatory actions in the past twenty-five years.
Personalized medicine, described by many speakers as a critical area for innovation in American health care, featured prominently in the discussion of drug and medical device regulation. In a closely related matter conference participants raised questions about safety, privacy, and standardization linked to greater use of genomic and proteomic data in diagnostics and therapeutics. Panelists also responded to questions regarding the role of expert advisory boards and conflict-of-interest guidelines.

QUESTION

How do you see pharmacogenomics being integrated with the regulatory process, and will it improve drug safety?

GALSON: We will not achieve a personalized medical system without scientific advances in pharmacogenomics. We have already approved drug products that will be paired with genetic testing devices to enable us to better predict in what person a drug will be most effective or in whom it might cause an adverse event. I believe pharmacogenomics is going to change fundamentally the way drugs are used, prescribed, and developed, but it is happening more slowly than people initially predicted.
**QUESTION**

Dr. Krall, as clinical trials are contracted out to various institutions and clinical research organizations, will genetic profiling become a part of the routine battery of tests and data collected for patients?

**KRALL:** GlaxoSmithKline and quite a few other companies are already doing routine pharmacogenetic profiling of patients in clinical trials and then banking the results. Last year approximately 65 percent of subjects in all GlaxoSmithKline’s trials agreed to provide such a sample. As Dr. Galson indicated, we are already able to identify prospectively patients predisposed to a certain characteristic response on the basis of either their genetic or metabolic profiles. I think we are going to see an acceleration of the value of genetic and other related kinds of profiling over the next ten years.

**GALSON:** The FDA faces enormous challenges in keeping pace with technological advances. We need a new type of expert who really understands the data collected through these profiling efforts, and we also need new types of information management systems capable of storing and analyzing enormous quantities of data. The FDA is already working to address these challenges. We have created some specific technical working groups and have hired people with the appropriate expertise. The FDA has also established initial guidelines to help inform companies of the kinds of data we seek and how we intend to use them.

**QUESTION**

How will all this information be standardized and by whom? How is this genetic information going to be both used and protected?

**GALSON:** Standardization is a critical element in enabling the use of the vast amounts of digitized health care information being generated today and is an issue that demands immediate attention. If what one
physician records as a blood pressure is not interpretable by another physician, then that information cannot be transferred from system to system. There are a number of organizations that are currently trying to establish standards for health care information. Health Level 7 (HL-7), for example, is a standards-developing organization accredited by the American National Standards Institute to operate in the health care arena. HL-7 brings together an international community of health care subject matter experts and information scientists who collaborate to create standards for the exchange, management, and integration of electronic health care information.

A number of health care institutions have figured out how to generate research databases from their data and then to mine them in order to update guidance for their practitioners. As we move forward, I am certain that data access and use will be the subject of much public concern, but I do believe it is possible to use genetic information while maintaining privacy.

**KRALL:** The privacy laws that currently govern the FDA’s ability to release and use data also apply to all pharmacogenomic data. We are not allowed to attach personal identifiers to this data and make it available to the public. We have to protect genetic information just as we protect all the other information we have.

**QUESTION**

I am an oncologist by training, and I am intrigued by the application of genomics and other primary data for cancer patients. We are not that far away from a situation where one might see, for example, a breast cancer patient with more than one specific mutation. We will be able to compile a genomic profile and identify three or four mutations that will allow a specific cocktail of drugs to be designed expressly for that patient. In light of these changes how do you see the existing regulatory paradigm progressing? It will not be possible to perform
an infinite number of clinical trials to find patients with all four of those specific mutations. It seems that we will have to rely on other methods.

I was also interested in Dr. Schultz’s comments about such surrogate markers as the “virtual family” and the extent to which laboratory tests can be used as evidence that a drug works. I know we are not there yet, but I would be interested in hearing your thoughts on where we are headed.

**SCHULTZ:** Since drugs are not my area of expertise, I cannot speak to your question in those terms. I do want to emphasize that when I talk about the “virtual family,” currently it is more a concept than a reality. I agree that the idea of being able to perform an individual clinical trial for each possible combination of genes and disease is not feasible. Simply put, we are going to have to devise a new paradigm, but we do not know exactly what it will look like. Regardless, it is imperative that we find a way of addressing the challenge. I anticipate that the Critical Path Initiative will help us in evaluating these products in a timely way, thereby enabling clinicians to make good choices that benefit their patients.

**GALSON:** This is an excellent question, even though there is no definitive answer. First, we have always used and continue to use surrogate markers to approve products when we think the markers are appropriate. A very challenging issue involves determining what it means to decide that a surrogate marker is appropriate for regulatory purposes. It will be increasingly important to develop additional techniques for reviewing and approving products, which means the agency will have to change. We must reexamine how we look at evidence and change the way we design and evaluate trials. Successfully executing these changes will continue to be one of the FDA’s greatest challenges. In addition to keeping pace with technological change, we must continue to refine our scientific methods and processes.
O’HOLLA: One of the strengths of the device industry has been in modeling performance. We are often faced with situations in which we have to evaluate a device that is made in a range of sizes. Each device may have different mechanical characteristics, but all operate in the same way. For those kinds of devices we have a successful track record to draw on. But as the industry begins to develop devices that influence human physiology in ways that are more than just mechanical, we will begin facing challenges similar to those of the drug industry.

GALSON: I would speculate that we are also going to be faced with the difficult problem of how to establish and accept evidence of effectiveness. We may find ourselves developing more single-patient trials that give us reasonable certainty concerning efficacy within a given type of patient, or we may move to much smaller groups of patients in order to make a determination about whether a drug is working within that group. All of this could happen without running a large-scale controlled experiment.

QUESTION

Well-designed clinical trials have typically been run on large populations with very narrow queries put against the clinical trial population, either for a drug or medical device. As those data sets become publicly available on the Web, other people can run queries against them for which they were not initially designed, producing some interesting results of unanticipated effects. I am curious to hear the panel’s commentary on the “side effect,” as it were, of making data so publicly available.

KRALL: I do not think it is a bad thing. It is good that people who are interested in having access to data can generate hypotheses on the basis of that data. The more ideas, the better for health care. Yet I will acknowledge that making those databases publicly available is fraught
with difficulties. It is easy to generate hypotheses without a thorough understanding of the underlying structure of the trial and the data it generated, meaning there is potential for the foundation on which hypotheses are made to be pretty poor. Still, I think it is better that the data be made available than kept private.

**GALSON:** Dr. Krall makes an excellent point. The world is marching in this direction, and it is beyond our control to stop it, even if we wanted to. In such an atmosphere it is particularly important that the FDA fulfill its commitment to make sure it is communicating as clearly as possible about what conclusions can and cannot be drawn from these databases.

**O’HOLLA:** A corollary point to this discussion is that as new data sets are made continuously available to everyone, the challenge will emerge to figure out when that data is “real information” and how to communicate it as quickly as possible without jumping to conclusions. The days of a stagnant label soon will be far behind us.

**QUESTION**

I would like to ask our two FDA center directors a question: if Congress were to give you discretionary funds to devote to the one thing in your incentives program that might have the most impact, what would it be? I would also like our industry representatives to respond.

**GALSON:** The single most important thing for us to be focusing on and the single thing that I am most worried about in light of budget cutbacks is keeping our staff expertise commensurate with advances in science. Scientific knowledge advances very quickly, and our staff will not be able to get adequate training until our agency accepts that it needs to bring in new people with relevant expertise. Unless the FDA can ensure the best possible scientific expertise, we will lose our distinction as world leaders in regulation.
SCHULTZ: In my experience managing the many sources of post-market information is very complicated. The greatest challenge that the Center for Devices and Radiological Health faces is trying to make sense out of all that information. That is where we need to put our efforts and our resources. Doing so certainly includes having and using the relevant expertise. It also includes effectively integrating information technology and the data-management tools necessary to cultivate that expertise.

O’HOLLA: I agree that the biggest challenge facing the device industry will be figuring out how to take data and turn it into information. In an atmosphere of continuous and fluid information, many decisions need to be made. When should we take action? What action do we take? When should we take no action? Money needs to be dedicated toward developing the regulatory paradigm most appropriate for effectively dealing with these questions.

KRALL: I think those at the FDA would benefit from investment in access to large-scale, epidemiologically oriented health information databases. Making this data available to the FDA will help us all acquire a better understanding of the impact of interventions in health care systems today.

QUESTION

The emphasis thus far has been on how the advance of science has improved health care, both from a device perspective and from a therapeutic agent perspective. Another major influence on health care in this country is our tort system, and I wondered if you would be willing to comment as individuals, not from the perspective of your companies and agencies, on whether you think that the tort system is actually facilitating the advance of health care or hindering it?

SCHULTZ: I think there are strengths and weaknesses. If you take the position that there is nothing good about it, it is certainly easy to poke
holes in the system. Unfortunately, when we have discussions about matters like this, people tend only to consider extreme solutions. As with most controversies, the truth lies somewhere in the middle and in the path toward moderation.

**HUTT:** The National Childhood Vaccine Injury Act (NCVIA), which was created in 1986 to reduce liability and respond to public health concerns about vaccine safety, could readily be applied to all pharmaceutical products, both drugs and devices. Under the NCVIA the National Vaccine Injury Compensation Program (NVICP) compensates those injured by vaccines on a “no fault” basis, meaning that people filing NVICP claims are not required to prove negligence on the part of the health care provider or manufacturer to receive compensation. Compensation for vaccines administered on or after 1 October 1988 is paid from the Vaccine Injury Compensation Trust Fund, funded from an excise tax on every dose of vaccine that is purchased. We must get rid of the Russian roulette approach to the tort law that we currently have, which is unquestionably a national disgrace.

**QUESTION**

Historically, expert advisory panels have played an important role in the FDA’s decision-making practices, and I would like the center directors in particular to discuss how they envision the role of such panels in the future.

**GALSON:** We rely on many outside experts that are hired on as “special government employees” so that they can review confidential data. Expert advisory panels are our version of the external peer review of the scientific community. They enable us to get outside input about decision making that takes place at the agency. Advisory panels are critical to the FDA, and I definitely see their involvement as continuing, if not growing. Dr. Schultz already told us about the program the Center for Devices and Radiological Health has implemented to bring
in outside experts. I would like to see efforts like that at the Center for Drug Evaluation and Research.

SCHULTZ: Advisory panels have been extremely valuable to the FDA. Sometimes concerns arise because panels can be less predictable than some companies would like, especially in terms of how they approach problems and the kinds of information they think are important. I think having experts, particularly clinical and statistical experts, come in and help us with our evaluations is an absolute imperative.

In terms of the future we are currently evaluating how to use the expertise of advisory panels across the product life cycle, especially in the postmarket arena. A recent report issued by the Heart Rhythm Society, for example, has made recommendations on how the FDA and industry can make better use of clinical expertise to evaluate not just premarket submissions but also postmarket events. We hope to begin implementing those recommendations in the near future.

One of the real challenges posed by expert advisory panels is the issue of conflict of interest. We need to find qualified experts who do not have conflicts; however, since many experts have career paths involving both public- and private-sector positions, this can be difficult.

O’HOLLA: Advisory panels definitely help the FDA with its decision making, but I am a little more concerned with how they operate today than I have been in the past. Increasingly, I see such panels impinging on either the responsibilities of manufacturers or of the FDA. It is important to make sure that panel members stay focused on their role as advisers and that we do not let them hijack the system.

KRALL: I am concerned about the discussion regarding conflict of interest, apparent or real, among members of an advisory panel. Concerns about conflict of interest have the potential to alienate the people best qualified to serve on those panels. It also puts the industry and the agency at odds with each other because we are forced to compete for the same expertise or expert advice, which is in nobody’s best
interest. I also often wonder whether we ask advisory panels questions at the right points in the drug development process. One of the things I have thought about for some time is whether we should ask advisory committees what they think of the program we are about to do rather than what they think of the program we have already finished.

**GALSON:** The work that we do is so important to people in the United States that there will always be controversy. We will always have advisory panels that provide us with recommendations, but it is important to emphasize they are just recommendations, some of which certain parties may not agree with. It is unrealistic to expect that advisory committees will reach conclusions that are pleasing to all stakeholders. I want to echo Dr. Krall’s point that the system is under threat now, and there are quite extreme views on how to define what constitutes a conflict of interest. If we define it too stringently, we will not be able to have experts on our panels who possess the depth of knowledge required to give us the advice we need.

**QUESTION**

Do you think the effort to harmonize with other countries has been helpful, or has it slowed down the influence of what the Critical Path Initiative is intending to do?

**GALSON:** I think harmonization is very difficult. Industry has often asserted that they need regulations to be harmonized around the world because they are global companies. Yet the fact is that countries around the world are different. Those of us who have participated in these harmonization efforts know how challenging the process is, but I do not see any way to avoid further efforts on this front. There will never be a single world government, nor will there be one world regulatory body. On the other hand, we have not let the challenges of harmonization prevent us from moving forward in important initiatives like Criti-
cal Path. If we had waited to try to harmonize Critical Path around the world or even just with Japan and Europe, the initiative would never have been launched. This is an example of how we try to be leaders worldwide. When we see something that needs to be done, we do it, even though it may take a lot of work. We cannot put off launching new initiatives and improvements because of the challenges posed by harmonization.

SCHULTZ: I certainly agree. Harmonization is a long, tedious process, but I do not see a conflict between harmonization and Critical Path. International standards offer examples where the FDA has participated in successful harmonization. To the extent that we have discussions regarding science and engineering, we can harmonize well, because those subjects cross borders fairly easily. Good science is good science and good engineering principles are good engineering principles. On the device side we have been able to make significant progress in those areas.

In terms of the expectation of success, if you demand a certain level of review and a certain level of oversight, that is what you are going to get. If expectations are not the same around the world, then trying to design a single regulatory system is going to be extremely difficult. Overall, it is not impossible, and I think we are slowly making progress. For example, the United States is accepting principles from other countries when they seem to be effective.

O’HOLLA: I think harmonization is a lofty and good goal to have, but I do not think that we will ever see true harmonization. Even as you harmonize your engineering principles, different scientists in different countries make different risk-benefit determinations. So you always have different decisions being made on the same set of data. That is where the challenge lies.

KRALL: We all sit on this globe because of gravity, but otherwise there is not much else that is the same. To me the fundamental challenge for
those of us who operate in this multinational world is to be agents of harmonization on behalf of patients. When we see something that is a benefit to a patient in Africa, Japan, Australia, or the United States, it is our responsibility to try and make that available for patients wherever they are. We will always be working through the lens of different regulations, different cultures, different medical practice, and different treatments.
III.

Food and Dietary Supplements Regulation
Food safety has been a compelling public health problem since ancient times, and events of recent decades have underscored the extent to which it remains so in the United States. There are almost eighty million cases of food-borne illness every year in this country, leading to hundreds of thousands of hospitalizations and many deaths. Although the public usually hears food safety being discussed only when a “newsworthy” outbreak captures the media’s attention, throughout its hundred-year history the FDA has been engaged in efforts to ensure the safety and security of the nation’s food supply.

In this chapter I discuss how issues surrounding food regulation—both high-profile and seemingly mundane—have been shaped by changes in scientific knowledge and social experience in the century following the passage of the 1906 Federal Food and Drugs Act. By doing so, I track associated shifts in the agency’s regulatory approach and point to some specific challenges regulators face today and in coming years.
The Role of Regulation

In the FDA’s early years the public’s attention centered on broad concerns about sanitation and filth. While it was clear that certain food adulterations could make one ill, the prevailing understanding of how or why food-borne illness occurred was different from the one we possess today. Specifically, early-twentieth-century regulators fixated on monitoring the chemical toxicants that had begun to be found in foods, often present in the form of such additives as heavy metals.

The FDA gradually acquired more authority, first with the passage of the Imported Milk Act in 1927, which mandated specific provisions for the fitness of milk not produced in the United States, and later with the Federal Food, Drug, and Cosmetic Act of 1938. In 1944 the Public Health Service Act further expanded the jurisdiction of the FDA, allowing it to take actions based on certain overwhelming public health needs not necessarily related to foods. This included, for example, the regulation of pet turtles known to transmit salmonella to children who handled them. Later laws, such as the Nutrition Label Education Act, the Dietary Supplement Labeling Education Act, and the Dietary Safety Health and Education Act, each of which contains provisions for education, have also served to make the agency’s regulatory activities more focused and strategic.

Changes in Knowledge

While new laws lead to changes in the way regulators must approach food safety, significant changes in knowledge influenced the nature of regulation itself. One major change during the past hundred years is that scientific knowledge has become much more widespread. It is no longer uncommon for a mainstream publication like *Time* to feature an article discussing microorganisms in food. Coverage of such a technical topic would not have appeared even just a few decades ago. It is not just increased public knowledge about science but also the na-
ture of scientific knowledge that is changing the way foods are regulated.

In fact, scientists did not link microorganisms to food poisoning until the early 1940s. One of the first individuals to establish this connection was the University of Chicago microbiologist Gale M. Dack, who theorized that ingesting bacteria could produce illness. Dack was so eager to test this theory that he used himself as an experimental subject, drinking a potent cocktail of *Staphylococcus aureus*.

Since Dack’s self-experimentation, food safety issues and the way scientists evaluate them have become much more sophisticated and refined, a trend also seen in the areas of medical devices and drugs. This is in part due to increased knowledge of risk by the public. Consumers are asking more questions and becoming more aware; they want to know more about their food. They have learned the names of various chemicals, although they do not always understand the associated risks, especially for very low exposures. Furthermore, consumers are focusing on specific hazards and on nutrition as they relate to chronic illness and its relationship to obesity. I predict there will be an increase in labeling as a result of this rise in public awareness of and concern with food safety.

Improvements to the field of epidemiology have had an especially notable impact on food regulation. People tend to think of food safety as simply testing foods. The tools available to epidemiologists, including those provided by the Centers for Disease Control and Prevention and the FDA, have evolved to the point where potential epidemics are being detected when just testing foodstuffs alone would miss them. For example, research in the field of molecular biology is enabling better assessment of attribution to food-borne illness. Molecular methods, such as DNA analysis of contaminating agents, are becoming important in efforts to identify outbreaks and their sources. It is no longer satisfactory to merely detect the presence of a contaminant like *Salmonella* in food. New molecular techniques are enabling us to match
the strain of *Salmonella* detected to a particular manufacturing plant and in some cases even to the specific processing line that produced the contaminated product. A recent study published in the *Journal of Food Protection* recounted an instance where real-time polymerase chain reaction detection was used to determine that mussels served at a particular Chinese buffet were the source of a food poisoning outbreak.¹

The specificity of such techniques will create unique situations for companies that manufacture, process, package, or even serve foods; it will definitely help us hold them more accountable.

In addition to being able to detect contaminants at the molecular level, scientists are learning about the pathogenicity and virulence of specific organisms. They have found that different strains of the same organism may vary greatly in virulence, and regulators are becoming sensitized to the implications of these variations for food safety. Food microbiologists have also been able to demonstrate that organisms thought incapable of growing in certain foods can in fact do so. For example, when the *Escherichia coli* 0157:87 strain was first detected in unpasteurized fruit juice in Washington State in October 1995, scientists who had assumed it was not possible for any form of *E. coli* to survive in acidified environments reacted with surprise and alarm.

These changes in scientific knowledge have also been accompanied by changes in technology. Innovations in aseptic processing technology have given us shelf-stable products in cardboard boxes. These new products can be confusing to consumers who are unable to distinguish the specially designed boxes from containers that have not been similarly processed. As a result there have been cases of botulism among consumers who mistook unprocessed cardboard packaging for the aseptic kind. Products that are able to remain on the shelf for as much as five times longer than traditionally packaged ones may nevertheless experience more microbial growth or allow for the emergence of a new type of microorganism that our bodies are unprepared to encounter. New food-borne pathogens, particularly those that
affect sensitive populations, as in the case of *Enterobacter sakazakii* in infant formula, compound the challenges faced by regulators.²

**Social Changes**

It is not merely the introduction of new scientific findings or technological innovations that have altered the regulatory terrain. Many new or so-called nontraditional foods have been associated with recent outbreaks of food-borne illness, reflecting dramatic demographic, economic, and social changes in the United States. We regularly eat foods like mangoes or almonds that would have been foreign to our grandparents. Shifting tastes and preferences require changes in how scientists look for organisms and contaminants. New foods, such as salsa—which recently surpassed ketchup in popularity—may be involved in food-borne illness but may not fit easily into our existing detection and monitoring systems.

Recently, an outbreak of illness connected to the popular Caribbean fruit mamcillo, known more commonly as mamay (*Mammea americana*), occurred in Florida. When the fruit was sent to FDA labs, it was unfamiliar to analysts. The methods used to analyze the mango, a related fruit, were found to be ineffective for analyzing the mamay. When the outbreak occurred, FDA microbiologists therefore had to quickly develop new methods specifically for mamay. Such scenarios, where research and new lab techniques are required on short notice to determine the source of a contaminating organism in unfamiliar foods, are becoming increasingly common.

More broadly, in recent years we have witnessed large-scale social changes that have significant implications for food safety and associated regulatory strategies. Demographically, Americans are growing older and increasingly rely on medicines, which may make them more susceptible to infections from food-borne organisms. Aging consumers are also eating different foods and possess greater nutritional awareness than previous generations. They are relying more on produce
and are seeking out raw, organic, and natural products as opposed to canned goods. Ironically, these changes in food choices are accompanied by migrations to urban centers where consumers become further disconnected from agriculture; many are shocked to see soil on lettuce in the produce section of the supermarket.

Related to these demographic shifts, foods increasingly are prepared outside the home in cafeterias, restaurants, and schools. The preparation and the handling of these foods are under someone else’s control, requiring consumers to rely on trustworthy behavior by food handlers. Not only must the individuals who prepare food be trusted, consumers must also feel confident that the FDA is setting and enforcing appropriate standards to ensure their health and well-being.

Not even two generations ago most food products were eaten close to the regions where they were produced. Recent increases in domestic and foreign transportation now enable foods to arrive from distant parts of the world. Patterns of economic development and land use in developing countries are changing rapidly as international trade in foods increases. Previously unused lands are being intensively cultivated, quite often by people who are not educated about sanitation and who may not engage in the same social habits practiced in the United States. Those foods will inevitably reach American consumers’ tables. International trade of food raises scientific and societal issues, but it also puts enormous stress on the resources of the FDA. If produce harvested in Mexico in the morning is eaten by someone in Los Angeles in the evening, opportunities for analysis or evaluation are seriously constrained. Even in the case of domestic produce distributed nationwide, such as lettuce or spinach grown in the Salinas Valley in California, any mistake made at the source becomes massively amplified.

The ease of international travel for business and tourism, which is currently at an all-time high and expected to increase over the next several decades, reflects another significant change in society. When
people travel, they are introduced to new types of food as well as new types of organisms, such as an unfamiliar parasite that may go unrecognized by an uninitiated American physician. As the United States increasingly becomes part of a global economy, once rare food-borne illnesses, such as those caused by *Cyclospora* infection, are becoming endemic in this country. Parasites that by the 1960s and 1970s were considered a problem experienced primarily in developing countries are once again appearing in the United States. At the same time our increased ability to detect such chemical contaminants as dioxins, as well as hormones and even such new organisms as the prions associated with mad cow disease, all challenge the risk-benefit ratios that regulators rely on to evaluate food safety. All these developments signal the need for dramatic change in the regulatory environment of the future.

**Rethinking Regulation**

Since the United States is part of a global economy and consumers and the food industry purchase food from other parts of the world, international agreements not only directly affect how the industry operates; they also impact domestic regulation. Such agreements include the North Atlantic Free Trade Agreement, the General Agreement on Tariffs and Trade, and such harmonization issues as Codex Alimentarius, which was created in 1963 by the Food and Agriculture Organization and the World Health Organization to develop food standards, guidelines, and codes of practice. The main purposes of the Codex program are to protect public health, ensure fair trade practices, and promote coordination of all food-standards work undertaken by international governmental and nongovernmental organizations. The outcomes of these meetings and agreements will directly affect how the FDA is able to function in the future.

Changes in the agency’s approach are going to drive shifts in regulation as we move further into the next century. When the FDA was
first created, regulators focused on a strategy of “command and control,” which involved outlining specific instructions for industry. For example, the pasteurized milk ordinance told milk producers exactly what temperatures to pasteurize, how long to pasteurize, and even at what slope to angle the pipe leading to the pasteurizer.

That approach has changed. A new philosophy of risk management is emerging, where the degree of regulatory control is seen as a function of the risk to public health. Consequently, quantitative risk assessments, where scientific data is used to estimate the impact of a given health issue, are becoming more common. Food safety objectives and performance standards will become a primary way by which the FDA maintains public health. The former involves determining the maximum level of illness society is willing to accept and working backward from that number to determine the amount of regulatory control necessary. Performance standards help communicate the maximum acceptable number of organisms allowed in food that do not undermine food safety objectives.

These objectives are not solely determined based on the findings of laboratory science; rather they are influenced by societal and political factors, which then guide the application of science in determining and setting standards. As a consequence regulators have become more concerned with whether or not manufacturers are able to achieve a desired outcome, rather than determining exactly how they do so. The same holds true for consumers, who remain intensely concerned with the safety of their food but relatively disinterested in how that safety is achieved. For example, with a few exceptions consumers do not appear aware of manufacturers’ increased reliance on such preventive technologies as irradiation of meat.

The events of 11 September 2001 have stimulated unprecedented changes in the realm of food security. Regulatory agencies especially have had to develop a different mindset about food defense. While the FDA has always been concerned with the tampering of foods,
never before have regulators been compelled to consider the possibility of a wide-scale, intentional, and massive poisoning of the public. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 has driven some of the most sweeping changes being implemented at the FDA. The act emerged as a response to the belief among politicians that the food system was susceptible to chemical or biological adulteration. According to a report prepared by the Food Policy Institute, however, the legislation’s goals may be difficult to reach. Members of industry are concerned about the “ability of a diverse food system to adapt to a control process that requires detailing the source of all ingredients and mapping these ingredients to products in wholesale or retail markets.”

The Food Allergen Label Consumer Protection Act of 2004 will also create new challenges for both industry and regulations. In a review of the food labels of randomly selected manufacturers of baked goods, ice cream, and candy in Minnesota and Wisconsin in 1999, the FDA found that 25 percent of sampled items failed to list peanuts or eggs as ingredients on their labels, despite containing these allergens. The 2004 act requires food manufacturers to state clearly whether a product contains any of the eight major food allergens responsible for over 90 percent of all allergic reactions. In addition, it requires that the FDA conduct inspections and issue a report within eighteen months to ensure that the food manufacturers comply with practices to reduce or eliminate cross-contact of a food with any major food allergen that is not an intentional ingredient in the food. This goal is ambitious, and it will be essential to work closely with industry to achieve compliance.

Conclusion

In summary the relationship between changes in scientific and societal knowledge, the demographics of our society, and regulatory philosophy will have a direct impact on how food safety is approached in
the decades to come. Intriguingly, both food imports and the demand for organic, locally grown produce are currently increasing. As a consequence, the greatest challenge facing the FDA will be to maintain a simultaneous focus on global and local issues. The agency must be able to monitor the safety of foreign products while also maintaining the security of those produced at home. Although the FDA cannot know what changes the next hundred years will bring, both technology and the regulatory environment will unquestionably continue to change in response to shifting public demands and changing habits of food consumption.

Endnotes


2. *Enterobacter sakazakii* is a rod-shaped bacterium that can cause sepsis, meningitis, or necrotizing enterocolitis in infants.


5. The eight major groups of food allergens include milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans.
Among the staunchest supporters of the Federal Food and Drugs Act of 1906 was Henry John Heinz, founder of the H. J. Heinz Company. In a marketplace where food products containing such fillers as leaves or wood fiber were commonly concealed within green glass jars, Heinz distinguished himself by producing unadulterated products, which he displayed in transparent bottles. Heinz knew that federal protections against adulteration and misbranding would be a great boon to producers of quality foods and to consumers in general; the regulatory regime imposed by the 1906 act proved highly effective and served to promote consumer trust in the food industry. It also helped establish the H. J. Heinz Company as an industry leader in food quality and safety.

Yet much as changes in society and technology have led to revisions of food and drug laws, a point made by Robert Brackett in the previous chapter, such changes have also affected Heinz and other members of the food industry. In recent decades consumers have become more interested in eating for health and often make efforts to choose foods that will help prevent illness. These shifts in dietary
habits, combined with advances in nutritional science, pose significant challenges both for the FDA and for industry. Interestingly, these issues largely will be played out in the small space of the food label.

In this chapter I examine how the wealth of data being generated by nutritional scientists is prompting a reconsideration of current approaches to food labeling. I offer a perspective from industry on fortification of foods and the FDA’s approach to mediating qualified health claims. A brief assessment of two recent studies conducted by the Women’s Health Initiative helps illustrate some of the issues complicating the process of making nutritional knowledge out of raw data.

The Woman’s Health Initiative studies also illuminate the potential for applying knowledge from the behavioral sciences to the food label. It is important to find ways to make valuable nutritional information available to consumers, but doing so requires attention to the presentation of that information. Those responsible for the contents of the food label need to develop a sophisticated understanding of how consumers use the label and interpret the nutritional information it provides.

Broad concerns about food safety and the globalization of the food supply underpin issues surrounding the regulation of food. I conclude this chapter by situating specific policy recommendations about labeling within this larger domain.

**Data and Diet**

Nutrition science is a young but prolific field. Recent investigations have identified the immune functions of vitamin D acting as a hormone, as well as a strong association between iron deficiency and some of the observed toxicities of lead. The scientific community is also continuously learning about the positive roles various botanicals may serve when included in the diet. A particularly compelling area of nutrition research concerns the fetal origins of adult disease, where epidemiologists have indicated that particular nutrients may have a
profound effect on embryonic development. As scientific research reveals the function of nutrients and their impact in the food supply, the FDA’s mode of communicating that information to consumers—the food label—must evolve as well.

With the enormous amount of data about food and nutrition now available, the FDA faces the challenge of prioritizing which findings warrant attention on the nutritional-facts panel of the food label. The existing facts panel already provides consumers with a variety of different types of information.

First, it indicates the amount per serving of saturated fat, cholesterol, dietary fiber, and “other nutrients of major health concern.” Yet as scientists report new findings about the connections between nutrients and health—including determinations that the relationship between dietary components is more complicated than initially understood—will these categories need to be reconsidered? Will it be possible to communicate what constitutes a nutrient “of major health concern” when that nutrient’s value comes via its connection to a different component of the diet? While it may be tempting to crowd the label with all these new findings, how much information is too much? When do consumers reach information overload? The increase in information available about nutrition should compel the FDA to reconsider what the existing label communicates and whether the current approach continues to be the most effective way to share knowledge about nutrition with consumers.

Second, the label currently provides nutrient reference values, expressed as “% daily values,” that “help consumers see how a food fits into an overall daily diet.” Increasingly, food companies are looking to fortify their products with potential bioactives in hopes of gaining a marketing edge. These claims are attached to many food products, and new competitors are appearing among the traditional vitamins and minerals. But, as I stated above, the nutritional science field is young, and food manufacturers are not in a position to evaluate the
long-term implications associated with enhancing the nutritional content of their particular products in the context of a food supply containing many other fortified products. Only the FDA has the objectivity necessary to consider the total diet and to determine what impact this rush to fortify might have on health. Nothing is more critical to the promotion of the health of our nation’s citizens and economy than ensuring the existence of a strong, honest arbiter.

A third significant and related feature of the FDA’s current approach to food labeling is that it allows claims about the relationship between a nutrient or food and a disease or health-related condition: for example, calcium helps prevent osteoporosis. According to the FDA the inclusion of these claims is meant to be “helpful to people who are concerned about eating foods that may help keep them healthier longer.” Other authors in this volume have pointed out that America’s health care system is increasingly oriented toward a prevention-focused model. While labeling will remain a critical mechanism for informing consumers about which food products may best help them preserve and protect health, the FDA must be vigilant and remain steadfast in the science when evaluating potential claims.

At Heinz we have been encouraged by the prudence shown by the FDA in its evaluation of preventive claims. The company witnessed the FDA’s commitment to science firsthand with the agency’s ruling on the qualified health claim for the benefits of tomatoes and tomato sauce in reducing the risk for prostate cancer. The FDA authorized the following statement for use on labels:

Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. FDA concludes that there is little scientific evidence supporting this claim.4

The rationale for the caution behind this ruling is found in the FDA’s meticulous review and interpretation of the scientific findings. The
exhaustive and thorough nature of the review process should inspire consumer confidence in the FDA’s approach to qualified health claims.

Science in Practice: The Women’s Health Initiative Studies

Two studies conducted recently by the Women’s Health Initiative exemplify the kind of research needed to advance the understanding of the relationship between diet and disease. Even well-designed studies, however, underscore the difficulty of establishing clear correlations among nutritional components, dietary habits, and health. The limitations inherent in the Women’s Health Initiative studies provide further support for the cautious review process that the FDA is using to evaluate qualified health claims.

Animal studies, observational data, and randomized controlled trials had previously indicated a possible increase in the efficacy of calcium by taking it with vitamin D supplements as a means of preventing fractures. When applied to a study involving more than 36,000 postmenopausal women, such supplementation resulted in a small but significant improvement in hip-bone density; however, it did not significantly reduce hip fracture and actually increased the risk for kidney stones. At the end of the trial approximately 75 percent of the women were still taking the study pills, but only 59 percent were taking the intended dose.5

Secondary analyses of the subgroup of adherent women—those participants who took at least 80 percent of their study medication—suggested a reduction in hip fractures. Even so, attempting to draw conclusions about efficacy based on secondary analyses in epidemiological studies has pitfalls. Further, many questions were left unanswered by the study. Was the vitamin D dose too low? Did the baseline levels of calcium and vitamin D influence the results? Was the trial structured correctly to detect a small effect?

Another Women’s Health Initiative study evaluated the impact of a low-fat dietary pattern on the risk for invasive breast cancer. Most
participants did not reach the stated goal of a diet with only 20 percent of calories from fat. Only about 33 percent of the women in the experimental group attained the goal in the first year of the study, and only 14 percent were still adhering to it by the sixth year.\(^6\)

Furthermore, the findings indicated that among postmenopausal women a low-fat dietary pattern did not result in a statistically significant reduction in risk for invasive breast cancer over the average eight-year follow-up period. A seemingly confounding finding indicated that women with a higher baseline fat intake showed a significantly reduced risk for breast cancer.

Despite their inherent limitations, these kinds of trials play an important role in enhancing the understanding of nutrition and health. Certainly, they demonstrate that when it comes to food and nutritional choices, there are no magic bullets. Positive effects on intermediate markers like cholesterol do not guarantee an effect on the endpoints of morbidity or mortality.

**Behavioral Science**

In addition to illustrating the difficulty involved with the interpretation of nutritional data, the Women’s Health Initiative studies also make clear that altering dietary behaviors is difficult. Literature from the behavioral sciences indicates that successful lifestyle changes require people to be psychologically prepared and committed. Each woman who participated in these studies received intensive intervention—help that is not often available to the general public. Most participants nevertheless still encountered difficulties in adhering to new routines and dietary changes. Even in a scenario where an individual has committed to making a change in dietary habits, a number of obstacles may hinder that change, including a lack of knowledge, skills, or support; an inability to weigh the benefits versus the drawbacks; or a combination of these factors.
In addition to ensuring that labeling decisions are informed by sound nutritional science, the FDA will need to collaborate with other scientific disciplines to make the nutrition label more relevant and accessible to consumers. I have observed that consumers frequently experience difficulty in assessing risk. Many researchers in the behavioral sciences are aware of this difficulty and have turned their attention toward understanding how consumers interpret and use information in pursuit of dietary goals.7

In creating a label that effectively integrates accurate nutritional information, it will be important to consider the messages that the label transmits and the implications of the label for consumer knowledge and interpretation of risk.8 Determining the most pertinent information to provide in the limited amount of space available on a food label will not be possible without understanding how consumers read labels and what they expect from them.

To add another layer of complexity to the psychology of nutrition, making short-term dietary changes is very different from maintaining those changes over the long term. While working as a hospital dietitian, I observed that the fear people experienced after surviving a heart attack often motivated them to make dietary changes. Yet, as they became increasingly removed from the health crisis, their motivation to maintain these healthier habits decreased. This same kind of “backsliding” can be seen in the Women’s Health Initiative study, where adherence to the study protocol varied considerably.

The FDA establishes its regulatory approach within this complicated and often counterintuitive context of people’s behavior. Members of industry can help support the agency’s approach by providing consumers with information about their products via the label and perhaps even aid consumers in acquiring some of the skills essential for eating well. If reducing the risk for chronic disease requires lifestyle changes, eating a healthy diet comes by making appropriate choices in the supermarket. The industry can provide a supportive environment
that offers choice, and it will be most effective if it does so in accordance with standards promulgated by the FDA.

The FDA has taken some initial action in this area by issuing a definition of what qualifies as “healthy.” Perhaps now is the time for the agency to develop a standardized visual logo that can result in quick, easy decisions for consumers who want to choose foods that help them follow dietary guidelines to reduce the risk for chronic disease. For example, while some companies have introduced their own logos directing consumers to specific foods, consumers might be better served if all companies used a single logo approved by the agency. Indeed, the FDA has expressed interest in knowing whether there are more effective formats for presenting the science supporting dietary claims than through the use of words alone.9

Industry is looking for leadership not only with regard to the food products that Americans use at home. Heinz is a company that derives nearly half of its North American revenue from the away-from-home eating segment and also foresees a growing consumer interest in nutrition of foods served in restaurants. As the baby-boom generation continues to age, its members will demand to know more about the foods they are consuming away from home. When the FDA issued its revamped nutrition label in the 1990s, food-service establishments were held exempt. Since consumers now spend about half of every food dollar on food eaten outside the home, the time has come to reexamine this approach.

Heinz’s consumer behavior research indicates that when consumers eat out, they often look for a balance of healthy and indulgent options. For example, when given an option, 70 percent of respondents indicated they would choose whole-grain breads. The majority would like to see more fruits and vegetables on the menu. Fat—not just total fat but also saturated and trans fat—is one of consumers’ main concerns. Even while the majority of respondents thought that food-service establishments should offer both healthy and indulgent menu
Taking a Closer Look at the Label

items, it is important to recognize that consumers may express certain dietary preferences in the context of a survey that do not match their actions.

The food choices people make are often context dependent, meaning sometimes they will select a healthier option and in other situations they will choose a more indulgent item. Heinz’s recent surveys of food-service operators show that health and nutrition are among their top ten concerns—after cost and labor issues. For manufacturers, providing food-service operators with clearer nutritional information can help them better accommodate patrons who value knowing the nutritional content of meals eaten away from home.

Food Safety and Globalization

The choices that consumers make with respect to individual food products—whether at home or in restaurants—are occurring in an atmosphere of collective anxiety about food safety. Advances in technology are increasingly enabling the detection of substances at ever more minuscule levels. The potential for unnecessary panic and alarm when a substance is identified but the clinical significance of the quantity is not known has become heightened with increases in the sensitivity of detection techniques. Consumers and members of industry need authoritative, evidence-based guidance on what measurements should be used to determine what levels of certain substances are safe to consume. To this end Heinz encourages the FDA to take the lead in establishing no-effect thresholds—standards to ensure that substances are not present in foods in quantities that pose threats to health—in order to help consumers assess risk.

Globalization of the food supply further complicates current issues about food and nutrition. While the globalization of food supply chains has enabled consumers to expect the availability of all kinds of foods year round, traceability has become a critical issue from both a
security and a health standpoint. When health issues arise or mislabeling occurs, the FDA must be able to act expediently.

The FDA also has a critical role to play in offering technical assistance to developing nations to help them build their own regulatory infrastructures. Not only will this promote food safety on a global basis, but for top-performing American companies it could also allow for greater access to important overseas markets. The FDA’s reputation for credibly setting and maintaining food safety standards is recognized around the world. The agency’s role as a leader will be an essential part of efforts to harmonize national and international food safety and nutrition labeling regulations. Forging collaborations with similar agencies in other countries will be critical to this process of opening global markets as well as to maximizing the efficient use of our nation’s own resources.

As the FDA enters its second century, it must continue to be visible and vocal while staying above the political fray in order to continue serving consumers and industry with integrity. Throughout its history the presence of a strong FDA has been crucial to the competitiveness of the food industry. The challenges that lie ahead are just as critical as those encountered by Henry John Heinz when consumers, government leaders, and enlightened members of industry recognized the need to provide the burgeoning packaged-food industry with a regulatory apparatus. At Heinz we stand ready to continue our partnership with the FDA.

Endnotes

2. Ibid.
3. Ibid.


7. The FDA has begun to recognize the importance of looking at the behavioral sciences. The synopses of consumer research on food labels findings indicate that consumers want labels that are simple and not highly quantitative and that include interpretive aids. See U.S. Food and Drug Administration, “Consumer Research on Food Labels,” www.cfsan.fda.gov/~lrd/ab-label.html (accessed 4 April 2007).

8. For example, in the 1997 Teisl and Levy article in the *Journal of Food Distribution Research* it was found that while nutrition labeling may significantly affect consumer purchase behavior, consumers may act as if they hold nutrient or health risk budgets. This means that while they may choose certain foods that are healthier—provided there is not a significant different in taste—they may then gravitate toward “unhealthy” products in categories where differences in taste are more noticeable. If this “substitution effect” is large, nutrient labeling may not change the overall consumption of “unhealthy” nutrients and may not lead to significant changes in health risk. See M. F. Teisl and A. S. Levy, “Does Nutrition Labeling Lead to Healthier Eating?” *Journal of Food Distribution Research* 3:28 (1997), 19–26.

For the past century advances in biomedicine have intertwined with approaches to monitoring and intervening in public health. One hundred years ago germ theory dominated the thinking about public health, and the presence of fillers and contaminants, including germs, gave consumers reason to be concerned about contaminated food and drugs. It is no coincidence then that the 1906 Federal Food and Drugs Act focused primarily on establishing standards for ensuring purity and quality of food and drugs; scientific and social issues that were prominent in the United States around the turn of the twentieth century greatly influenced the FDA’s formation and its early priorities.

As science and technology have yielded new understandings of health and illness, new laws have expanded some areas of the FDA’s regulatory authority. Ensuring the safety of the food and drug supply remains a key commitment, but the recent introduction of new products, including many novel dietary supplements, and advances in our knowledge of the relationship between dietary supplements and
health has prompted the FDA to reformulate its regulatory strategy in this area.

In this chapter I argue that the current challenges the FDA faces in regulating dietary supplements reflect a long legacy of the interrelationship of science and public health, one that extends back to the bacteriological revolution of the late nineteenth century. Examining the connections between the history of science and public health policy can help orient us in the present and point us toward the future. To this end I first provide a brief chronology of major efforts to apply science to public health problems.

I then outline the provisions of the pieces of legislation that most directly affect the regulation of dietary supplements today, the Nutrition Labeling and Education Act (NLEA) and the Dietary Supplement Health and Education Act (DSHEA). This legislation has been developed to address two pervasive challenges in the FDA’s efforts to regulate supplements: defining what qualifies as a supplement and determining how to evaluate the nature of claims that can be used to promote dietary supplements. Situating the FDA’s current regulatory strategy within the broader context of the history of scientific engagement with health and nutrition provides a platform for contemplating the future, and I conclude with some discussion and speculation about what lies ahead.

**Historical Perspective on Science and Public Health**

Louis Pasteur’s famous late-nineteenth-century experiments in which he cultivated microorganisms in nutrient broths helped depose spontaneous generation as the dominant theory of the origin of disease. His experiments laid the groundwork for the germ theory, which provided public health officials in France and other countries with an understanding of how to control or mitigate the growth of microorganisms. Public works improvements in sanitation and hygiene soon
followed. The U.S. and European governments also moved to monitor and regulate industry; in fact, the 1906 act put the United States in the vanguard of a broader regulatory trend.

In 1912 the Polish-born American biochemist Casimir Funk published what he called the “vitamine” theory of disease. The term *vitamine* was derived from *vita* (Latin for *life*) and *amino* (a group of organic compounds containing a univalent nitrogen radical). When it was subsequently discovered that not all vitamines included amines, the *e* was dropped. While germ theory focused on contaminants that might be present in food or water, vitamin theory held that it was the absence of certain compounds from food and water that led to disease. Research by the public health service epidemiologist Joseph Goldberger on the cause of the disease pellagra bolstered the vitamin theory.¹ Unlike many of his contemporaries, Goldberger theorized that pellagra’s prevalence in the southern regions of the United States was not due to the presence of a germ in the food supply. Through observations at a Georgia asylum and two Mississippi orphanages he determined that diet was at the root of the sickness. Historians have pointed out that it was the rise of new technologies for processing food, such as cereal grain mills, that helped make manifest such connections between dietary deficiencies and disease.² While the vitamin theory did not obviate germ theory, its emergence demonstrated the extent to which scientists and public health officials had underestimated the complexity of issues connected to health and illness.

The 1930s and 1940s represented a remarkable period of discovery in the realm of nutrition science. As more vitamins were identified and synthesized, scientists began to focus on the importance of vitamins, minerals, and amino acids in nutrition. Several Nobel prizes were awarded for such discoveries.³ Much as the dominance of germ theory had influenced the focus of the 1906 act, scientists’ evolving interests in understanding the complex array of nutrients essential for maintaining health and reducing the occurrence of dietary deficien-
cies were part of the context in which the Federal Food, Drug, and Cosmetic Act of 1938 was written.

Scientists working in the post–World War II era next began to associate the risk for certain chronic conditions, such as cardiovascular disease and cancer, with dietary and lifestyle factors. The studies of Ancel Keyes in the 1960s that demonstrated the significant contribution of saturated fatty acids to heart disease, along with reports from Sir Richard Doll confirming that smoking caused cancer, established a broader link between lifestyle and disease. As the evidence accumulated, manufacturers of certain foods began to recognize the commercial potential in making claims about the health benefits of their products, often via the label. As these claims became more pervasive, so did concerns about how to ensure their validity. In fact, the question of how to regulate such claims effectively continues to challenge the FDA.

In 1976 the Senate Select Committee on Nutrition and Human Needs published the bluntly titled report *Diet Related to Killer Diseases*, which highlighted the association of diets high in fat, saturated fat, cholesterol, and sodium and low in fiber with heart disease and certain types of cancer. Regulators found the results so compelling that the next year the Senate published its *Dietary Goals for the United States*, which defined a “target and healthy” diet for Americans and stressed eating foods in their natural and unrefined state. In 1980, the first set of “Dietary Guidelines for Americans” appeared. Published every five years since by the Department of Health and Human Services and the U.S. Department of Agriculture, the guidelines emphasize how good dietary habits can promote health and reduce the risk for major chronic diseases.

By the end of the 1980s nutrient deficiencies had been replaced by dietary excess as the preeminent threat to public health. Two major reports, the 1988 Surgeon General’s Report on Nutrition and Health and the National Academy of Sciences’ 1989 report *Diet and Health: Implications*
for Reducing Chronic Disease both pointed to the central role of diet and lifestyle in maintaining health. Increased emphasis on the preventive aspects of health refocused attention on supplements and how to define them in relation to foods and drugs.

This brief glimpse into the shifting relationship between scientific developments and public health initiatives reveals that despite significant advances in the knowledge of health and nutrition, the role of government in providing health advice has been complicated and at times contested. The history of nutritional supplements, particularly in the period between the passage of the 1938 law and NLEA in 1990, is primarily characterized by ambiguity surrounding whether they should be regulated as foods, drugs, or another category entirely. In the following two sections I explain how the legacy of this ambiguity is being negotiated today.

**Defining Dietary Supplements**

Two significant and persistent challenges in regulating dietary supplements have been defining what qualifies as a supplement and the nature of claims acceptable for use in their marketing. Although these issues have been identified at several points in the past, they were not resolved until the end of the twentieth century through new legislation.

Passed in 1990, NLEA aimed to make nutrition information available to consumers in a manner that would reduce confusion about nutrient content claims and facilitate healthy dietary choices. The law was also designed to prevent the appearance of unfounded health claims on food packaging, provide manufacturers with incentives to improve food quality, and make healthier options available to consumers.

NLEA mandated that manufacturers include nutrient information on food labels and permitted nutrient content and health claims based on “significant scientific agreement.” This does not require universal scientific agreement on the validity of a health claim but rather that a
body of consistent, relevant evidence from well-designed studies in humans must be available to support the claim. While defining what constitutes significant scientific agreement has posed an ongoing challenge to regulators, the enduring impact of NLEA can be seen today on the nutrition facts panel present on all food labels, as well as through the authorization of health and nutrient content claims. The act addressed nutrition labeling for conventional food and to some extent laid the groundwork for the more focused dietary supplement legislation enacted with Congress’s passage of DSHEA in 1994.

Like NLEA, DSHEA was also enacted to satisfy multiple goals. First, it brought a further measure of clarity to the issue of determining what constituted a dietary supplement. DSHEA placed dietary supplements in a special category under the general umbrella of foods, not drugs, and required that such supplements be specifically identified on the label. This law defined supplements in statute as any product taken by mouth containing dietary ingredients, including

products (other than tobacco) intended to supplement the diet that bear or contain one or more dietary ingredients. A supplement can be a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite constituent, or any combination of any ingredient mentioned above.7

Forms of dietary supplements can include extracts of concentrates, tablets, capsules, softgels, gelcaps, liquids, or powders; they are labeled as dietary supplements and not represented for use as a sole item of a meal or of the diet. With DSHEA as the legal framework regulators have put forward a strategy to elucidate the boundaries between dietary supplements, foods, and drugs.8

Under DSHEA firms are responsible for determining that the supplements they manufacture or distribute are safe and for establishing the truthfulness of representations or claims. Dietary supplements
do not need approval from the FDA before they are marketed; however, a premarket notification process exists for new dietary ingredients. Provisions for new dietary ingredients were developed because of the recognition that scientific discovery will inevitably lead to the presence of new products on the market. As such, DSHEA required that ingredients not already on the market before 15 October 1994 were to be defined as new dietary ingredients and were subject to specific regulation. Because no authoritative list of dietary ingredients marketed before this date exists (often referred to as pre-DSHEA dietary ingredients), it is the manufacturer’s responsibility to determine whether a dietary ingredient is in fact “new.” In addition, the manufacturer must be certain that the product containing the new dietary ingredient is a dietary supplement. Finally, unless the new dietary ingredient has previously been recognized as a food substance and is already present in the food supply, the manufacturer (and distributor) must demonstrate to the FDA why the new ingredient is expected to be safe for use in a dietary supplement.

As the FDA’s approach to regulating new dietary ingredients continues to evolve, incorporating stakeholder feedback is essential. In 2004 a public meeting was held to solicit comments from industry and consumers concerning the content and format for new dietary ingredient notifications. One of the strongest concerns focused on the lack of an FDA-authorized list of pre-DSHEA dietary ingredients, an issue to which the agency is attuned. Yet developing clear determinations of what constitutes a new or existing dietary ingredient is an ongoing effort—one that is further complicated by the challenge of evaluating the nature of the claims manufacturers of these products make.

**Evaluating Claims**

Four broad types of claims are used in food labeling: dietary guidance statements, nutrition support statements that include structure-function claims, nutrient content claims, and health claims. The first
two types do not require any premarket action by the FDA; manufacturers are responsible for the scientific substantiation to support those claims and for ensuring that the claim is truthful and not misleading. When structure-function claims are made for dietary supplements, the FDA should be notified within thirty days of the marketing of the product. If the FDA has a concern (e.g., the claim makes reference to curing, treating, or mitigating a disease or the product is not a dietary supplement), the manufacturer is informed in writing, and the notification is filed with comment in FDA dockets; otherwise the notification is filed in FDA dockets without comment. This notification process differs significantly from the process for health claims for which the agency reviews the scientific evidence for the claim and the type of claim language, if any, that is supported by the evidence.

Nutrient content claims characterize the level of a nutrient or dietary substance in a product. Generally, nutrient content claims use such terms as *free, high,* and *low,* or they compare the level of a nutrient in one food to that of another, using such terms as *more, reduced,* and *lite.* A nutrient content claim, on the one hand, could describe milk as “high in calcium.” Health claims, on the other hand, describe the relationship between a food and a disease or a health-related condition. Health claims are concerned with reducing the risk for disease, not with treating, mitigating, preventing, or curing it. For example, the statement that “diets high in calcium may reduce the risk for osteoporosis” is a health claim. Dietary supplements can also make health claims if the product meets the criteria to be eligible to bear the claim.

Based on decisions made by the Washington, D.C., District Court of Appeals in 1999, the category of qualified health claims for which the evidence is not well enough established to meet the significant scientific agreement standard indicated in NLEA was introduced for certain dietary supplements. These types of claims use disclaimers to indicate the strength of the scientific evidence and are regulated through enforcement discretion letters.
The FDA’s 2003 Consumer Health Information for Better Nutrition Initiative outlines the use of qualified health claims when there is emerging evidence for a relationship between a food or dietary supplement and reduced risk for a disease or health-related condition. When the agency reviews such claims, regulators must identify the evidence that is most useful for evaluating a substance-disease relationship. Once all the relevant evidence has been compiled, the agency must determine whether credible scientific evidence exists for the claim. If the answer is no, then the claim is denied. If the answer is yes, then the level of scientific evidence is evaluated or ranked.

One way to think about these claims is on a continuum of scientific evidence, with the highest level being scientific consensus. Significant scientific agreement is indicated by a body of consistent, relevant evidence from well-designed clinical or epidemiological studies, and, if the evidence meets this standard, the FDA will initiate rule making to authorize a claim. If the body of credible evidence does not meet the significant scientific agreement standard, the FDA uses its enforcement discretion for a qualified health claim. A letter of enforcement discretion for a qualified health claim will contain the qualifying language for which the FDA will consider its enforcement discretion. For example, certain claims must explicitly state that the FDA has determined that evidence is very limited and preliminary or that the benefit is highly unlikely or highly uncertain.

The FDA continues to research appropriate qualifying language for claims in order to give consumers a practical understanding of the different levels of supporting science. The agency is also interested in finding better formats for presenting this information to the general public. As we move toward a preventive and personalized model of health care, it is increasingly vital that consumers be able to interpret nutritional information easily and correctly to make informed dietary choices.
The Future of Regulation

In contemplating the future of dietary supplement regulation at least three trends need to be considered. The first involves the enormous growth of the dietary supplement industry. When DSHEA was first passed, the FDA received very few new dietary ingredient notifications. In 2006 the agency will evaluate submissions of over fifty new dietary ingredients. This growth suggests that more products are being made available to consumers. A second trend involves continued interest in the use of health claims for conventional foods as well as dietary supplements. Food and nutrition conferences typically report numerous studies exploring potential relationships between food components and various diseases. The research indicates a continued interest in promoting foods for health but often without understanding of the nature of evidence needed to substantiate a relationship between a substance and reduction of disease risk. The third trend comes out of a new shift in scientific thinking about health and nutrition based on our increasing understanding of the interaction between genetic profiles and metabolism.

In light of these trends our society is faced with interesting questions of what steps will be taken in the future to reduce health care costs by focusing more resources on reducing the risk for disease. Will these efforts result in research that can be translated into meaningful information that consumers will trust? Will different types of information on food products and dietary supplements be needed so consumers can more effectively meet the needs of their individual genetic and metabolic profiles? Or will attempts to reduce health care costs through diet and lifestyle modifications fail because the tools available to consumers are inadequate?

Avoiding this unfortunate latter scenario requires modernizing labeling information. Updating the label, in turn, requires research support for the development of substantiated health claims as well as
an investment in tailored education initiatives—both of which are on the FDA’s agenda. As the FDA continues to learn about the relationship between diet and disease, its approach to public health will inevitably require further change. In a shifting scientific landscape the FDA will continue to take seriously the challenge of defining what constitutes a dietary supplement and its safe use by consumers, and how to determine the validity of health claims. With a firm understanding of the past, the FDA has begun to anticipate and prepare for what the future holds.

Endnotes

1. Pellagra (an Italian word meaning “angry skin”) manifests itself in lesions of the skin and mucous membranes, gastrointestinal symptoms, neurological derangement, and mental confusion.


3. For example, the 1937 Nobel Prize in Chemistry was shared by Paul Karrer for his investigations on carotenoids, flavins, and vitamins A and B2, and Sir Walter Norman Haworth for his investigations on carbohydrates and vitamin C.


7. The complete statutory definition of a dietary supplement can be found in section 201(ff) of the Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. 321).


9. Dietary supplements do not include products approved or authorized for investigation as drugs, certified antibiotics, or licensed biologics.

Chapter 11

Regulation at a Crossroads

The FDA and the Future of the Dietary Supplement Industry

Steven Mister

Of all the consumer and medical products regulated by the FDA, dietary supplements are the most recent to achieve the status of a unique class of products subject to unique regulation. With the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994, dietary supplements became their own regulatory category—regulated in many ways like traditional food but also subject to separate requirements. As a result of DSHEA many entrepreneurs seized the opportunity to launch start-up ventures in this relatively young economic sector during the mid- and late 1990s, bringing a host of new players into the marketplace. Along with the vibrancy and atmosphere of innovation that often characterizes an emergent industry comes great variation in the behavior of individual manufacturers. Most members of the dietary supplement industry are eager to embrace the regulatory framework they see as essential to sustaining growth and consumer confidence, while a few act in ways that are shortsighted and even potentially detrimental to the industry as a whole.
The dietary supplement industry is at a crossroads, and it remains to be seen what future direction it will take as the marketplace matures. Will consumer confidence and use grow as manufacturers choose to emphasize the role of good nutrition and supplementation in preventing disease and promoting health? Or will the unscrupulous manufacturing practices and the outlandish advertising of a few rogue players erode consumer trust in dietary supplements? That direction will be determined not only by the manufacturers themselves but also by the FDA’s involvement and willingness to regulate responsibly.

In this chapter I begin with a historical perspective that illuminates how the dietary supplement industry arrived at this crossroads. Looking toward the future, I then outline four significant interrelated factors poised to influence the way the industry is regulated and its future path. In light of those factors I conclude by describing several regulatory issues on which the FDA must focus in order to fulfill its commitment to protect the health and safety of consumers who are using dietary supplements.

**A Brief History of Dietary Supplement Regulation**

The first vitamins were isolated in 1911, just five years after passage of the Federal Food and Drugs Act of 1906. At that time the 1906 act defined foods as “articles used for food, drink, confectionary, or condiment by man or other animals, whether simple, mixed, or compound” and drugs as “any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease in either man or other animals.” Appropriately, the drug definition included an important parenthetical acknowledgment that foods affect the structure and function of the body. Determining that a product was misbranded required the FDA to identify “false statements about ingredients,” and the burden of proving adulteration in either food or drugs was placed on the government.¹

¹
In the 1920s, as new vitamins were being identified with increasing frequency, more and more consumers began to recognize them as beneficial. By the time the 1938 Federal Food, Drug, and Cosmetic Act was passed, American consumer interest in taking vitamin pills and capsules to prevent illnesses and to promote health was impossible to ignore. Under the 1938 act the definition of a drug was broadened to include “articles . . . intended to affect the structure or function of the body,” and diagnosis and treatment were now under FDA oversight. Dietary products intended for the nutritional needs of infants and the disabled were placed under the umbrella of foods “for special dietary use.” Shortly thereafter the FDA set up a vitamin division to address the problems posed by unscrupulous manufacturers who marketed subpotent ingredients or improperly labeled their products. Nevertheless, such problems persisted in the industry.2

In the 1948 decision United States v. Sullivan, which considered the case of a retail druggist in Columbus, Georgia, who had resold sulfathiazole tablets (used to treat a range of bacterial infections, including gonorrhea) without including the required directions for use or health warnings, the Supreme Court determined that the FDA’s jurisdiction extended to retail distribution.3 As a result pamphlets distributed to consumers and vendors promoting the health benefits of vitamins, minerals, and herbs were now considered “labeling” and therefore subject to FDA jurisdiction.

The continued relevance of labeling was demonstrated when the Federal Trade Commission’s Fair Packaging and Labeling Act sparked controversy in 1966. First, this act sought to require warning labels on supplements, stipulating that vitamins and minerals were already present in commonly available foods. Second, it would have banned product labels from making health claims about dietary deficiencies. Third, it defined any supplements with potencies exceeding 150 percent of the recommended daily allowance as drugs, a move widely
interpreted as an effort to restrict consumer access to larger-dose vitamins and minerals.

Consumers who had come to value dietary supplements as an essential part of their diets were outraged. Over the next decade Congress was inundated with nearly one million letters expressing opposition to the act. This consumer activism culminated in the Proxmire Amendment, signed into law in 1976 as part of the National Heart, Lung and Blood Institute Act. Viewed by consumers and members of industry alike as a victory for the dietary supplement industry, the amendment defined vitamins and minerals as “increasing the total dietary intake” and stated that they “could not be classified as drugs simply due to their potency.” It also permitted vitamins and minerals to be sold in a variety of forms, including in combinations within foods. The amendment’s overall effect was to limit the FDA’s authority to regulate dietary supplements, at least when they contained vitamins or minerals. This was not the last time that a tremendous groundswell of consumer activism would persuade Congress to revisit and revise proposed regulatory initiatives by the FDA.

Despite conflicting messages about the benefits of supplementation, consumers have increasingly recognized a link between better nutrition through supplementation and better health. In 1978 a federal court opined that consumers were “wasting millions of dollars annually on the purchase of vitamin and mineral preparations which they either do not need at all or do not need in the potencies or combinations that are being bought.” In spite of this admonition National Health and Nutrition Examination Survey data indicates that supplement use only increased in the years following that warning, from 30 percent of the public using supplements on a regular basis in the 1970s to 55 percent by 1990.

In recognition of this increased consumer use of dietary supplements Congress passed the Nutrition Labeling and Education Act in
1990. The act included a provision to establish a separate procedure for the pre-approval of health claims made for dietary supplements. When the FDA failed to publish promptly a preliminary draft of its nutritional labeling regulations, consumers became concerned that the agency was ignoring the congressional directive. Instead the agency announced enforcement plans to treat supplements as unapproved new food additives.

Consumers’ murmurs of discontent soon escalated to an outcry. Leading up to the passage of DSHEA in 1994, Congress received more mail regarding dietary supplements than on any other issue since the Vietnam War. Protection of consumer access to supplements as well as information about their uses was underscored by DSHEA. At the same time the new law defined, in statute, the term dietary supplements; established a safety requirement for “new dietary ingredients” (those dietary ingredients not already on the market at the passage of DSHEA); authorized the creation of separate regulations for good manufacturing practices that would be unique to dietary supplements; and provided new methods for the FDA to remove unsafe products from the market.

Curiously, more than twelve years after DSHEA’s passage the media often mistakenly report that dietary supplements are not regulated by the FDA, that there are no requirements for supplement manufacturing, and that supplement advertising and labeling are unregulated. These inaccuracies must be as frustrating for the FDA, which does indeed regulate dietary supplements under the auspices of DSHEA, as it is for members of the industry.

Perhaps this confusion over the regulatory status of supplements is caused by the fact that the vast majority of amendments to the 1938 Federal Food, Drug, and Cosmetic Act have been precipitated by public health crises to which Congress responded by enhancing the FDA’s regulatory authority. Dietary supplements appear to be an exception
to this historical rule; changes to the 1938 act that relate to dietary supplements have more typically followed FDA action that would limit consumer access or restrict information. Regulation of supplements has evolved into a complex interplay in which a variety of stakeholders actively engage in the regulatory process by submitting comments and by attending public meetings held by the FDA to ensure their voices are heard. Despite the common misperception to the contrary, the dietary supplement industry is regulated today. A number of significant factors are poised to affect the way in which it will be regulated in the future.

**Factors Influencing the Regulation of Dietary Supplements**

As occurred with regulation of food, changes in scientific knowledge and in society are poised to influence the trajectory of the dietary supplement industry. Idamarie Laquatra noted in chapter 9 that increases in the amount of research generated by the nutritional sciences and the nature of that data are prompting reconsideration of the FDA’s approach to regulating food. Developing appropriate academic research methods for dietary supplements is the first factor with important implications for their labeling and marketing and even their composition.

Unlike the traditional food industry, the unique positioning of dietary supplement regulation—falling between the requirements for foods and drugs—reflects the current knowledge gaps about dietary supplements and may impede the rate at which research on the issues is conducted and findings are disseminated and applied. Although many manufacturers of dietary supplements sponsor and conduct research on the safety and benefits of their products, just like their pharmaceutical colleagues, there is a significant disparity in financial incentives to do so. Because most dietary supplements are naturally occurring, manufacturers do not receive marketing exclusivity and cannot make
proprietary claims for active ingredients; while dietary supplements may be extracted or concentrated in proprietary ways, they all begin with a naturally occurring molecule and therefore do not enjoy the same degree of patent protection as a molecule created in a lab. Even if research determined to FDA satisfaction, for example, that vitamin E prevents cardiovascular disease or that omega-3 fatty acids significantly reduce the risk for cancer, no manufacturer could establish a proprietary claim on either compound.

Furthermore, the way in which dietary supplements should be studied in a clinical setting is different from pharmaceuticals. A double-blind, randomized, placebo-controlled clinical trial that examines a molecule’s effect in isolation, long heralded as the “gold standard” for drugs, may not be appropriate for supplements. The law does not permit supplement manufacturers to label their products as cures or treatments for disease, so why study them in the same way we study disease? Studying prevention is more difficult and may require more long-term follow-up of the participants, larger sample sizes, and more careful analyses to rule out confounding influences. Several of the problems associated with clinical trials for dietary supplements can be illustrated by a recent study conducted by the Women’s Health Initiative to observe the relationship between calcium and vitamin D in preventing bone fractures. First, because researchers felt that instructing women to cease their regular regimen of calcium supplementation was unethical, many women who were assigned to the placebo-controlled group were independently and intentionally incorporating high amounts of calcium into their diets. Second, the pre-existing high calcium intake of these women may account for the small differences observed between the placebo group and those in the “intent-to-treat” calcium and vitamin D cohort related to bone density and other outcome measures. Third, intent-to-treat is a method of including all randomized subjects’ data in an analysis, regardless of their level of compliance; this means that members of the cohort may not
have been taking their supplements as prescribed. For all these reasons actual calcium intake between the placebo and study groups may not have been materially different.

To direct attention to gaps in current research the National Institutes of Health recently held a “State of the Science” conference focusing on multivitamin and multimineral products. Meetings like this may help stimulate additional research into the use of supplements. At the same time, however, the refusal of meeting organizers to consider research from nonrandomized, controlled clinical trials in developing conclusions about the relationship of supplements to disease prevention demonstrates a lack of appreciation for observational data, cohort studies, epidemiological research, and similar tools that help explain the links between nutrition and good health. Although research in the area of dietary supplements requires attention to different parameters, it is no less important, less rigorous, or less scientific than clinical trials of pharmaceuticals.

The financing of health care for an aging American population will be a second significant influence on the future of the dietary supplements industry. Today’s baby boomers are going to live longer and healthier lives than their parents. They are very interested in maintaining good health; this is the first generation of mothers who told their children to take their vitamins every day and then also took them themselves. Dietary supplements have the potential to support a preventive approach to health, a trend evident in medicine in general. But more high-quality scientific data is needed to understand the combinations and circumstances of use that provide the greatest benefits. Determining how to undertake research demonstrating the efficacy of dietary supplements for preventing illness and improving health and wellness will be an important aspect of efforts to ease financial pressures on our health care system that are exacerbated by a large, aging population.
Indeed, health care costs in the United States in 1999 amounted to $1.2 trillion, or 13 percent of the nation’s gross domestic product. Quite literally, people cannot afford to be sick and increasingly are turning to disease prevention. Numerous studies have sought to quantify the economic value of specific nutritional supplements that prevent suffering and reduce mortality. For example, the routine use of multivitamin and mineral supplements by the elderly could improve immune function and thus reduce the occurrence of infectious disease. The potential benefits and cost savings of improved nutrition are substantial. To this end members of industry and regulators must work together to foster behavioral change, including suggesting regular supplement use among key population subgroups.

Another factor that will influence future regulation of the dietary supplement industry is standardization in our increasingly global economy. With developing countries positioned to serve as new markets for existing dietary supplement products, the FDA’s active participation in harmonization efforts like Codex Alimentarius, a joint Food and Agriculture Organization–World Health Organization program to ensure fair trade practices and promote international coordination of food standards, is critical. The principles embodied in DSHEA, if applied internationally, will allow consumers everywhere to enjoy the benefits of a wide array of dietary supplements manufactured by a worldwide industry that is committed to consumer health and safety.

A global economy also means increased competition from Asia in raw ingredients, which is putting new pressure on manufacturers to source their materials less expensively. Widely accepted analytical methods must be developed to identify the bioactive markers and the physiologically relevant components of dietary ingredients so consumers can be confident that they are buying high-quality supplements. Likewise, testing and validation of ingredients to prevent adulteration or contamination—either inadvertent or intentional—must be developed and required. In an era when ingredients are sourced globally,
rigorous testing and accountability at all stages of the manufacturing process is imperative.

The final factor influencing future regulation of dietary supplements is that this industry is coming of age in an information era. When DSHEA was enacted more than a dozen years ago, no one anticipated the impact the Internet would have on consumers’ ability to access health information. The ability of consumers to retrieve information about their own health, alternative medical treatments, and strategies for prevention have come with an empowerment and a desire for consumers to take more control over their health care decisions. Nor did anyone fathom the proliferation of misleading and quasi-scientific advertising campaigns for dubious products. The FDA needs to develop a better understanding of how consumers access and evaluate medical information and make a greater effort to track and evaluate products whose labels make false or misleading claims.

Clearly, the dietary supplement industry, while vibrant, is in flux. Factors that include scientific research, the costs associated with supporting a large and aging population, our globalizing economy, and the rise of the Internet are all converging to provide a larger role for dietary supplements. But those same factors also present challenges—ones that can be most effectively overcome with clear guidance from the FDA.

The Role of the FDA

When negotiating the challenges posed by these factors, the FDA does not have to create a new regulatory paradigm. In fact, the statutory and regulatory framework envisioned by DSHEA can serve both consumers and the dietary supplement industry well if it is robustly and fairly implemented and enforced.

When assessing a given dietary supplement, the FDA should evaluate the safety of the dietary supplement and earnestly pursue manufacturers whose products do not offer that assurance. Under DSHEA,
once a product is marketed, the FDA is responsible for showing that a
dietary supplement is unsafe before it can take action to restrict the
product’s use or remove it from the market. In the case of new dietary
ingredients, manufacturers must submit a petition demonstrating the
safety of the ingredient. Imagine the dilemma faced by a company
whose new dietary ingredient petition is rejected because in the FDA’s
opinion it has failed to provide adequate premarket review safety data,
while a competitor that has not made the effort to file the petition goes
to market with the same ingredient. The former is penalized for seek-
ing to comply with FDA regulations, while the latter is rewarded fi-
nancially for eschewing the procedure. As responsible members of the
supplements industry work to demonstrate that new dietary ingredi-
ents are safe for consumption, we need both guidance and enforce-
ment from the FDA that provide for consumer safety while leveling
the playing field for competitors.

Postmarket analysis, including adverse-event reporting, is also es-
seential for the safe marketing of dietary supplements. For the last sev-
eral years the industry has been supporting legislation that would
require dietary supplement manufacturers to report adverse events to
the FDA. The Dietary Supplement and Nonprescription Drug Con-
sumer Protection Act was recently enacted by Congress. The act will
require that supplement labels include a telephone number or address
for consumers to report serious adverse events and that manufactur-
ers share these reports with the FDA within fifteen days. Consumers
must have confidence that when they report a serious problem with a
product to its manufacturer, the information will be shared with the
government agency that oversees these products. Adverse-event re-
porting data will be most effective when it is collected and analyzed by
the FDA, a single authority that can evaluate reports from the entire
industry.

First, the FDA should also take action to ensure high quality of
dietary supplements. Although there are several programs for volun-
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tary certification and seals of approval, they are not adequate substitutes for formal good manufacturing practices that are specific to dietary supplements. These practices for dietary supplements were authorized by DSHEA, but more than twelve years later the industry has yet to see a final ruling on this issue. Responsible companies that impose high standards, processes, and certifications continue to be put at a competitive disadvantage vis-à-vis their noncompliant peers. The issuance and robust enforcement of good manufacturing practices would ensure greater adherence to quality control across the industry. Responsible companies in the dietary supplement industry believe that promulgation and enforcement of good manufacturing practices for dietary supplements is the single most critical thing the FDA can do to improve and ensure the quality of supplement products.

Second, although the agency is not charged with demonstrating the efficacy of dietary supplements, it is charged with the authority to require manufacturers to substantiate the claims they make regarding benefits. In the case of health claims (those that purport to help reduce the risk for disease) the FDA must approve them before they can be used in labeling. By carefully evaluating the scientific basis for full and qualified health claims, the agency is already taking steps that will help maintain the integrity of the industry. Moving forward, it will be important for the FDA and manufacturers to collaborate in order to develop claims that are both accurate and accessible to consumers and to establish processes for the approval of claims that are transparent and predictable and that fairly evaluate the data.

Finally, other government agencies, the Federal Trade Commission (FTC) in particular, should continue to monitor the supplement industry and insist that advertising for these products is truthful, substantiated with credible scientific evidence, and not misleading to consumers. The FTC should apply the same criteria and standards as it does in other forms of consumer advertising. Through an agreement between the two agencies the FTC has jurisdiction for dietary
supplement advertising, while the FDA exercises jurisdiction over labeling of these products. Although the two agencies enforce different laws with respect to these two arenas (the FTC is less interested in the difference between health claims, structure-function claims, and nutrient content claims, for example, and is instead focused on whether the statements are indeed truthful), they have a shared mission to ensure that consumers get accurate information to inform their purchase decisions. The two agencies must continue to collaborate to monitor product claims.

**Conclusion**

The future holds great promise for dietary supplements. Decisions that manufacturers and regulators make with regard to research into product effectiveness and efforts to harness the beneficial potential of supplements to address the increasingly costly health care needs of a large, aging population will have important consequences for the industry. The FDA has the opportunity to assume a leadership role in international standardization efforts, while also establishing controls over claims made in the virtual domain of the Internet.

The dietary supplement industry, though strong and vibrant, is currently at a critical crossroads. To ensure that it continues on the proper path—one that helps meet the health needs of consumers worldwide—manufacturers need regulatory guidance from a robust, proactive agency. With the FDA’s support the dietary supplement industry can flourish in a manner that helps alleviate pressing health issues.

**Endnotes**

7. See also Laquatra, chapter 9 of this volume. The study’s findings were initially published as Rebecca D. Jackson et al., “Calcium plus Vitamin D Supplementation and the Risk of Fractures,” *New England Journal of Medicine* 354:7 (16 Feb. 2006), 669–683.
Chapter 12

Second Discussion Session

Food and Dietary Supplement Regulation

The regulation of food and dietary supplements is based on labeling controls. In recent decades a move has been made from abstract models for how consumers read labels to more sophisticated studies of consumer behavior in reading and interpreting nutritional information. Participants in the discussion of food and dietary supplement regulation were especially interested in gaining a clearer sense of the FDA’s future regulatory strategy for supplements as well as learning how individual centers within the agency assess the effectiveness of their educational initiatives. The nature of intra-agency collaboration and cooperation with regard to the management of food safety issues also came to the fore.

QUESTION

I have seen nutraceuticals defined as natural bioactive chemical compounds that have health-promoting, disease-preventing, or medicinal properties. Within the FDA’s regulatory framework are nutraceuticals considered foods or drugs?

SCHNEEMAN: The FDA does not currently have a formal regulatory definition for nutraceuticals. A careful evaluation of the nature of the claim being made is often our most effective strategy for determining the appropriate regulatory action for a given product. We need to ask whether the product in question is a food that has been modified or a
drug for which statements are being made about its use in treating, mitigating, curing, or preventing disease while delivering nutritional content. Answers to these questions will determine whether the product should be regulated as a food or a drug.

**QUESTION**

My question concerns efforts to improve the effectiveness of the food label. Manufacturers sometimes compensate for reductions in the fat content of their products by increasing sugar, which potentially negates any health benefit. In Europe color-coded symbols—a red “stop” light for foods high in sugar and a green “go” light for foods with lower sugar contents—are used as an easy way to inform consumers about the sugar content of certain products. In the United States I do not believe food labels provide a recommended percent daily value for sugar. Is the FDA planning any action to ensure labels carry more detailed information about sugar content? More specifically, has the agency considered employing visual symbols to do so?

**SCHNEEMAN:** A consumer can obtain information in many ways from the nutritional-facts panel that must appear on all food labels. Currently, a percent daily value for total carbohydrates is provided. The limitation of the kind of system you suggest is that it would only inform the consumer about the total sugar content. For example, both fruits and milk contain sugar. The existing ingredient list provides information about what contributes to the total sugar content, but we have found that consumers are more likely to be interested in the amount of added sugar. Looking at the ingredient list enables consumers to see which types of sugars are being used in the formulation of the product in question.

**QUESTION**

Dr. Laquatra, I am curious to know whether your observation of supermarket consumers, which you drew on in your discussion of the
potential role of the behavioral sciences in shaping regulation, revealed that customers were reading the labels on the products they purchased?

**LAQUATRA:** Usually they were not. Consumers do not tend to linger in the supermarket unless there is entertainment such as a kiosk where they can sample products. In general, once consumers locate the products they regularly purchase, their primary concern is obtaining them as quickly as possible. Interestingly, I have found that parents are more likely to read labels of foods intended for their children than for themselves.

**SCHNEEMAN:** Consumer research indicates that consumers are most likely to look at the label when they first choose a food product. Once they have become familiar with that product, they do not appear to review the label with every subsequent purchase. We certainly hope that consumers spend time looking at labels at home, but without knowing a consumer’s shopping pattern or familiarity with a given product, it is difficult to assess how consumers use label information.

**LAQUATRA:** Research from the International Food Information Health Service shows that people often look at the label to determine calorie content, although many do not know how many calories they require per day. This indicates a knowledge gap among consumers about how to use label information. I believe we can do more to increase the knowledge and skills consumers bring to their evaluation of food products.

**QUESTION**

Where on the spectrum of regulation do homeopathic remedies fall? Similarly, how do you regulate products that claim to be homeopathic but that do not follow the original definition of such a remedy?

**HUTT:** The origin of the FDA’s regulation of homeopathic drugs stems from the fact that the man who shepherded the Federal Food, Drug, and Cosmetic Act of 1938 through Congress, Senator Royal Copeland
was a homeopathic physician. He ensured that references to the U.S. pharmacopoeia as well as the homeopathic pharmacopoeia were included in the statute.

In the post–World War II period the prominence of homeopathic remedies declined precipitously. In 1972 the FDA began to consider a review of over-the-counter drugs, and the question arose as to whether it should include homeopathic drugs. The FDA dispatched inspectors nationwide to assess the size of the market for homeopathic drugs and whether it was justified in bringing homeopathic drugs under regulation. The inspectors identified only five homeopathic pharmacies in the entire United States—two in Los Angeles and three in the Bronx. Thus, the FDA concluded that homeopathic remedies would be excluded from a review of over-the-counter drugs. One consequence was a subsequent growth of homeopathy, which has now become a billion-dollar-per-year industry.

SCHNEEMAN: Today, as with nutraceuticals, our regulatory action for homeopathics is dependent on the nature of the claim being made. Claims about reducing risk are allowed for dietary supplements and foods. In fact, some of the qualified health claim petitions we have received have been denied because the evidence presented was associated with treatment or mitigation of disease, which placed them in the category of a drug claim. If homeopathic products are making treatment or mitigation claims, then they should be regulated as drugs, not as dietary supplements.

QUESTION

Do you feel that the existing statutes provide you, as regulators, with sufficient authority to ensure the quality of our foods and dietary supplements?

BRACKETT: The 1938 Food, Drug, and Cosmetic Act and part of DSHEA have endowed us with substantial authority. With respect to
DSHEA we have yet to implement all the powers accorded to us by the law, such as the authority to issue good manufacturing practice guidelines for dietary supplements.

Yet we could indeed request enhanced authority. Mandatory recall authority, which would empower the FDA to order manufacturers to recall products deemed unsafe, is often suggested. However, in practice such authority would be superfluous because most manufacturers do not hesitate to take recall action in response to safety concerns voiced by the public.

**SCHNEEMAN:** I agree with Dr. Brackett that we must make efforts to take advantage of the authority already granted to us by the law. In the realm of dietary supplements it is true that both the Nutrition Label Education Act (NLEA) and the Dietary Safety Health and Education Act (DSHEA) include provisions for education. But one of the greatest challenges facing the agency is the ability to dedicate resources to education effectively.

We have heard much about the potential of the genomic revolution to reform health care costs, but that requires an investment from the FDA as well as other federal agencies. Educating consumers is vital to realizing those benefits. The huge potential that exists to improve the quality of health care will remain untapped if we do not take action to make sure that consumers have the skills to use the nutrition labeling information that is currently available to them.

**QUESTION**

Dr. Schneeman, in your reply to the previous question you seem to suggest that the FDA has not been as effective as possible in implementing the education components of acts like NLEA. How does the agency assess effectiveness?

**SCHNEEMAN:** Today most of our efforts in education have been implemented via the Internet. One example of a new program that we hope
to make available on our Web site is specifically focused on weight management using tools for evaluating nutrition labeling. We also know that many consumers possess a degree of awareness of the label’s nutritional-facts panel. Almost all consumers have some awareness of that component of the label, but there is definitely room for improvement.

In just the past two years we have begun to work more closely with the existing education programs at the Center for Food Safety and Applied Nutrition (CFSAN) that are concerned with safety. These programs had established valuable connections with a number of secondary schools, so we are tapping into the existing network of science teachers, in particular, to integrate more dietary information into their curriculum. We have also played a very active role in the development of the Dietary Guidelines for Americans. As a result instructions for using the label are now more prominent among the guideline’s educational materials.

In terms of evaluating effectiveness, CFSAN frequently conducts surveys. One of the items we have been tracking is awareness of information about fat. Specifically, we are interested in learning whether consumers are aware of the information about fat content provided on the food label, as well as what it means in terms of reducing the risk for heart disease. Survey results indicate a significant increase in awareness and understanding of trans-fatty acids and their association with heart disease. Consumers are also successfully distinguishing between different types of fat. Our data reveal a substantial increase in awareness of the health risks associated with saturated facts as well as the health benefits of including omega-3 fatty acids in the diet. We are also currently preparing to publish the mid-year progress report for a program called Healthy People 2010, which proposes a set of health objectives for the nation to achieve over the first decade of the twenty-first century. The initiative includes metrics to measure progress over time.
BRACKETT: I want to add that the FDA centers are not the only organizations involved with evaluating the success of educational programs. The National Institutes of Health also conducts consumer behavior studies.

QUESTION

Dr. Brackett, do you feel that the FDA needs to strengthen its relationship with the U.S. Department of Agriculture (USDA)?

BRACKETT: The CFSAN has a very good relationship with the USDA. We work very closely with their Agricultural Research Service, which does much important research on our behalf. If it appears we are at cross-purposes with the USDA's Food Safety Inspection Service—with whom we have a significant amount of overlap—it is more an artifact of the authority granted them under the Meat and Poultry Inspection Act as opposed to ours within the 1938 Federal Food, Drug, and Cosmetics Act. Whenever we are engaged in developing guidance or regulations, we consult with the USDA to prevent adverse effects on their activities.

I do feel that we need to build a better relationship with the USDA's Agricultural Marketing Service to ensure we are consistent in our messages to farmers about safety. Until about ten years ago produce-borne illness was detected very infrequently. As our surveillance techniques have improved, we are finding that fresh fruits and vegetables are often associated with food-borne illness. Collaboration may be the key to mitigating the public health impact of such illness, and we are already engaged in efforts to improve intra-agency communication.

LAQUATRA: While the FDA and the USDA have different mandates and authority, as Dr. Brackett indicated, there are many opportunities for cooperation. In the area of nutrition the Department of Health and Human Services and the USDA have collaborated on the Dietary Guidelines for Americans. Further, any educational materials that are
released through the federal government have to go through dietary guidance review, which is one means by which consistency of messages between Health and Human Services and the USDA can be ensured.

**QUESTION**

Steven Mister, in your presentation you talked about how a “rogue element” in the nutritional supplement industry is contributing to an environment where more responsible members of industry are placed at a competitive disadvantage. Do you believe more effective enforcement action from the FDA would help to level the playing field?

**MISTER:** Think about many of the infomercials that air after midnight or on Sunday mornings when a half hour of airtime is inexpensive to purchase. Think about the ads in popular women’s magazines that make outrageous claims about weight loss. Those kinds of claims are also made on the labels of the products. I think the biggest problem for the dietary supplement industry’s future growth in this country is the lack of consumer confidence that these kinds of products and advertisements engender.

A core group is devoted to dietary supplements. Those are the people that wrote to Congress in the early 1970s to prevent restrictions on the sale of dietary supplements and again in the 1990s to support DSHEA. Those are the people who already believe steadfastly in the benefits of dietary supplements. In order for the industry to grow the way it should, Americans need to understand the benefits of supplements and have confidence in their effectiveness. That will not happen as long as they continue to see outrageous claims that they know cannot be true, nor will it happen as long as there are products available that are not subject to rigorous testing.

For example, the pharmacologically active component of a particular herbal may only be found in the root of a plant. Yet certain
companies are selling the leaves and stems. The company that manufactures the finished product is buying that raw material and labeling it as the herbal. When the consumers who purchase that product do not experience the expected benefits, they may dismiss the entire category of dietary supplements as ineffective. Greater enforcement by the FDA will ultimately drive the growth of the industry, and there is much the agency can do to help consumers obtain accurate information and ensure they are using effective products.
IV.

Conclusion
Chapter 13

Navigating the Molecular Revolution

*FDA Leadership in a Time of Transition*

Andrew C. von Eschenbach

As other authors in this volume have emphasized, a significant health care transition currently under way is changing the FDA, the industries it regulates, and consumers’ lives. For thousands of years medicine was practiced based on a very macroscopic perspective of disease. The understanding of disease processes—and even the definitions of them—were derived from what could be determined with the five senses. Around the time the FDA was founded, biomedicine went through a transition from a macroscopic perspective to a microscopic one. For the first time scientists could see the cells that composed a tumor and the microbes responsible for an infection and for tainted foods. While that transition was indeed dramatic, it was eclipsed by the most profound change to occur in the history of medicine. In the middle of the twentieth century DNA, the genetic code of life, was discovered, sending biomedical science on a journey of innovation that today is unraveling the most basic mechanisms of life and the root causes of disease processes.

Fueled by such progress, about ten years ago the health care field crossed a threshold from macroscopic-microscopic medicine and
entered the molecular era, positioning our society on the precipice of a genomic and proteomic revolution. As a society we are beginning to appreciate more fully the incredible opportunities, as well as implications, that are emerging from scientists’ attention to questions about the fundamental nature of life. This movement from the macroscopic to the microscopic to the molecular is more than a transformation. It is a metamorphosis, provoking us to envision a future that no more resembles the past than a butterfly looks like a caterpillar.

As the FDA embraces this dramatic change, it must remain focused on its core value of placing the health and safety of patients and the public at the center of everything it does. The FDA’s practice of decision making based on science underpinned its role in setting standards for the safety and efficacy of a range of products used by Americans and millions of people worldwide in the twentieth century. The FDA’s grounding in science has made it possible for Americans not to worry about the food they eat, to use medical devices without questioning their safety and effectiveness, and to be able to wake in the middle of the night and confidently take medication or, even more important, to give that medication to their children or grandchildren.

The world around the FDA is changing as the twenty-first century of molecular medicine unfolds. For the agency to maintain its status as the gold standard, the FDA itself must also change. Even in an era of declining budgets the FDA has recognized the importance of modernizing and transforming operations to address emerging needs and opportunities. The agency must align and adapt how it regulates and recognize the importance of its leadership role in the metamorphosis that will define our biomolecular era.

More specifically, the FDA must accept and commit to the rapid transformation of health and of health care in this country by establishing itself as the bridge that supports new molecular-based interventions as they move across the discovery, development, and delivery
continuum. Those interventions and solutions will not only include drugs, biologics, and devices but also food, which provides molecular nutrients integral to health. Several authors in this volume pointed to the role that nutrition education will play in empowering consumers to make choices that will help preserve health and prevent illness. The FDA will support that form of consumer empowerment as a part of maintaining its commitment to promote health and protect the public.

The agency is engaged in an ongoing process to redeploy resources strategically to address high-risk public health challenges. And as a science-led regulatory agency, the FDA has initiated the Critical Path to New Medical Products, a program designed to modernize and ensure more efficient development and clinical use of medical products. The FDA considers the Critical Path Initiative to be its top science policy effort for at least the next five years and expects its implementation will better integrate modern science and technology with twenty-first-century medicine.

The projects affiliated with the Critical Path Initiative, discussed in many of the preceding chapters, are intended to help provide the FDA with the tools necessary for effective leadership in the modern “-omics” era of genes, proteins, and metabolites. Under the initiative the FDA anticipates being able to increase the success rate dramatically in providing patients with innovative solutions that strike an optimal balance of high benefit and low risk because they are “personalized.”

Several specific projects that promise to help the FDA transform the way it brings new solutions to patients are already under way. The Oncology Biomarker Qualification Initiative, which represents collaboration among the primary research, evaluation, approval, and medical treatment delivery and reimbursement divisions of the U.S. Department of Health and Human Services—including the FDA, the National Cancer Institute, and the Center for Medicare and Medicaid Services—
offers one example of a key Critical Path project. It is intended to facilitate the identification of biomarkers, which are measurable characteristics that reflect physiological or disease processes. Biomarkers can be used to predict or monitor responses to therapy. Without clinically proven biomarkers and innovative trial designs, government, academia, and industry cannot modernize medical product development and realize the potential of a personalized system of medicine. Indeed, the capabilities promised by advances in genomics and proteomics indicate that the health care system of the future will be not only personalized but also predictive, preemptive, and more participatory.

The health care system of the future will be personalized by developing a sophisticated understanding not only of the disease process but also of the individual patient. In understanding both the disease and the person at the molecular level physicians will be able to provide treatment options uniquely suited to a patient’s particular needs. Instead of empirically prescribing a pill and hoping it works, patients will receive treatments designed specifically for them. Physicians will use the new tools of molecular medicine to develop unique individualized interventions, and through the very process of molecularly monitored delivery to patients the understanding of the biology of disease in individual humans will be elucidated. In this way delivery will itself become a platform of discovery.

Product development is at the core of the innovation process. The fruits of the tremendous explosion in innovation that has been occurring in biomedical research will only have been reaped when they are translated into actual interventions that can be applied to patients. Looking to the future, I envision an FDA that will be not only a science-based regulatory agency but also a science-led facilitating agency—one that helps new products travel across the bridge of development more rapidly and efficiently while ensuring their highest quality.
Technological innovations will also make this health care system predictive and therefore preemptive. Long before physicians ever prescribe a treatment, biomarkers will be used to predict whether that intervention will achieve the desired outcome. Reliance on such molecular tools, rather than on the current, limited phenotypic understanding of disease, will help preempt illness, fostering the shift from therapeutic models of treatment to a model more focused on prevention.

Finally, I expect that this health care system will be much more participatory. Increased utilization of information technologies and improved communication strategies will allow patients to assume a substantially more active role in their health care. It will be important for those at the FDA to consider how to work together with doctors and patients to make sure that they have the greatest opportunity to maximize the benefits of new medical products in a way that preserves their ability to make individualized choices free from restrictive burdens and that the data derived from health care can be used to further enhance the safety and effectiveness of these products.

Trends of personalization, prediction, and prevention are asserting themselves in the public’s understanding of food and nutrition. Much as people have become able to use their knowledge about food and nutrition to determine the most appropriate dietary practices for their own bodies and lifestyles, the decisions people will make about health care will be based on a similar kind of individualized knowledge.

Improving the efficiency and reliability of clinical trials in a period of rapid advances in science is another important priority for the agency. While it is not a member, the FDA is serving in an important oversight role for the Predictive Safety Testing Consortia, which includes representatives from Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, and Schering-Plough. Members of the consortium are interested in sharing their knowledge and databases related to toxicity and biomarker utilization. These biomarkers
will enable prediction of risks before treatments are applied and will also enable detection of warning signs, predictors, and indicators of toxicity or adverse events at the earliest stages of medical intervention. Using the modern tools of both the biological and information sciences, the FDA will be able to streamline and improve its approval process and enhance its postmarketing surveillance to protect the health and welfare of the patients it serves.

Despite recent innovations, many serious and life-threatening diseases still lack effective treatments. The path from cutting-edge medical discovery to the delivery of safe, effective treatments is long, arduous, and uncertain. Products fail before they reach the market either because clinical trials do not adequately demonstrate safety or efficacy or because they cannot be manufactured at a consistently high quality. However, even well-designed trials often do not yield extensive information about product performance.

The Predictive Safety Testing Consortia thus represents a major step toward transforming the future of health and health care in this country. Industry collaboration under FDA leadership provides an opportunity to move away from redundant testing and wasteful procedures toward new approaches. In this effort, as in many others, the FDA has an enormous opportunity and leadership responsibility. In taking these steps the FDA will retain all the rigor, discipline, and precision of regulation, but its efforts will be geared toward accelerating the rate at which new, beneficial innovations can be approved to the advantage of the public.

The FDA’s common purpose is to serve the public, who look to the agency not simply for the discovery of new genes or for credible information about the health care implications of new drugs but also for solutions to their health problems. Solutions in the molecular era must be integrated, but the FDA alone cannot coordinate this broad range of activity. The FDA’s leadership will come in defining how partnerships should work, evaluating results, and developing guide-
lines on the use of new approaches that researchers find effective. To facilitate completion of projects in a timely manner, the FDA will continue to bring together partnerships and consortia. Coordination in leadership is essential to illuminate the pathway to an era of personalized medicine, when doctors will be able to prevent—or even eliminate—dozens of today’s most devastating diseases.

The FDA is committed to creating a world where the right patient will receive the right intervention for the right reason, delivered at the right time and to the right location to attain the predictable right outcome that physicians will measure in real time. Our society has no choice about the metamorphosis of health care, which is already under way; however, unlike the caterpillar, our society does have a choice about what health care will become. Whereas it is easy to envision what might potentially be achieved, it will require a shared commitment across our society to make it happen.

Molecular science is already presenting health care regulators, health care providers, and patients with an enormous amount of data as well as with the challenge of turning that raw information into useful knowledge. Therefore, it is essential that the FDA immediately move to the rapid implementation of effective information technology infrastructures that will facilitate and enable the agency’s work. Science and medicine are intimately interconnected. Sharing data and information needs to be coordinated and integrated into a much more seamless network. Through integration and collaboration health care providers and regulators and patients can influence the outcome of the change process.

For as long as I have the privilege of leading the FDA, I look forward to collaborating and cooperating with all the other components engaged in this metamorphosis. Collectively, government and industry can fulfill their primary responsibility: to serve the public, whose lives, welfare, and health are dependent on them. The challenges facing the FDA range across nutrition, drugs, devices, and
biologics—for humans, as well as for the animals and pets under our care. The FDA must be a good steward of the resources it has at its disposal and must innovate in order to meet the demands of its incredibly diverse and complex portfolio. I believe that technology will help even as it continues to provide great challenges. I look forward to continued dialogue and discussions—not just about ends and purposes but also about how to achieve ends most rapidly and effectively.

The perspectives brought together in this volume show that regulators and industry have already embarked on the transformation of medicine and health care. In 2056, the year that will mark the 150th anniversary of the FDA, the regulation of food, drugs, medical devices, cosmetics, nutritional supplements, and other consumer goods will rely on different testing and monitoring technologies; will involve deeper collaborations with manufacturers, providers, and consumers; and yet will have retained the same core goal of ensuring the health and wellness of both individuals and the public.

Endnote

About the Contributors

Robert E. Brackett is the director of the FDA Center for Food Safety and Applied Nutrition (CFSAN). He received his B.S. in bacteriology and his M.S. and Ph.D. in food microbiology from the University of Wisconsin–Madison. He provides executive leadership to CFSAN’s development and implementation of programs and policies regulating the composition, quality, safety, and labeling of foods, food and color additives, dietary supplements, and cosmetics. Before coming to the FDA, Brackett was a professor of food science and technology in the Center for Food Safety at the University of Georgia and was also on the faculty of North Carolina State University, where he served as extension food safety specialist and assistant professor. He is a member of several professional societies and a fellow of both the American Academy of Microbiology and the International Association for Food Protection, and has served as a member of the editorial boards for *Applied and Environmental Microbiology*, the *Journal of Food Science*, and the *Journal of Food Protection*. Brackett has published more than two hundred scientific publications and has received numerous awards for his contributions and achievements.

Steven K. Galson is the director of the FDA Center for Drug Evaluation and Research (CDER). Galson holds a B.S. from Stony Brook University, an M.D. from Mt. Sinai School of Medicine, and an M.P.H. from the Harvard School of Public Health. He provides leadership for CDER’s broad national and international programs in pharmaceutical regulation. Galson has held senior-level positions at the Environmental Protection Agency, the Department of Energy, and the
Department of Health and Human Services. Prior to his arrival at the FDA, Galson was the director of the EPA’s Office of Science Coordination and Policy in the Office of Prevention, Pesticides, and Toxic Substances. He is the recipient of numerous U.S. Public Health Service awards, including the Outstanding Service Medal for his leadership and management of CDER while serving as acting center director from November 2001 to February 2002. He is also the recipient of three Secretary of Energy Gold Awards. Galson is a board member of the National Board of Medical Examiners and a regular peer reviewer for medical journals.

Peter Barton Hutt is a senior counsel in the Washington, D.C., law firm of Covington & Burling, specializing in food and drug law and trade association law. He was chief counsel for the FDA from 1971 to 1975. Since 1994 he has taught a course on food and drug law at both Harvard and Stanford law schools. He has served on a variety of roundtables and advisory committees, including the Institute of Medicine Roundtable for the Development of Drugs and Vaccines against AIDS, the Advisory Committee to the Director of the National Institutes of Health (NIH), the National Academy of Sciences Committee on Research Training in the Biomedical and Behavioral Sciences, the National Institutes of Health Advisory Committee to Review the Guidelines for Recombinant DNA Research, the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, and five advisory panels for the Office of Technology Assessment. Hutt has served on the Institute of Medicine’s Executive Committee and the panel on the Administrative Restructuring of the NIH, and he is presently legal counsel to the Society for Risk Analysis and the American College of Toxicology. He is coauthor of *Food and Drug Law: Cases and Materials* and over a hundred other publications.

Ronald Krall is senior vice president and chief medical officer for GlaxoSmithKline (GSK). Krall earned a bachelor’s degree in mathe-
matics from Swarthmore College and his M.D. from the University of Pittsburgh. He trained as a staff associate at the National Institutes of Health Epilepsy Branch and completed his training in neurology and clinical pharmacology at the University of Rochester. Krall is responsible for all matters of human safety for all GSK compounds in development and FDA-approved medicinal and vaccine products, and for pharmaceutical regulatory affairs and compliance with FDA good practice guidelines. Before joining GSK he held positions at AstraZeneca Pharmaceuticals, Abbott Laboratories, and Lorex Pharmaceuticals. He is a former member of the board of directors of the National Sleep Foundation, a member of the board of directors of the Delaware Valley Science Fairs, and a past trustee of the American Academy of Pharmaceutical Physicians.

Idamarie Laquatra is director of Global Nutrition at H. J. Heinz Company. She earned her graduate degrees in nutrition from Pennsylvania State University. A licensed registered dietitian, Laquatra has experience in the clinical, academic, and business fields. Prior to earning her advanced degrees Laquatra worked as a clinical dietitian in hospital and nursing home settings. After completing her Ph.D., she became a postdoctoral fellow in preventive cardiology at the University of Medicine and Dentistry of New Jersey. In 1984 she was employed as nutritionist for Heinz USA and subsequently became manager of nutrition for Weight Watchers Food Company. After brief stints in the consulting industry she rejoined Heinz as director of global nutrition in 2005. Laquatra is an active member of the American Dietetic Association (ADA), served as president of the Pittsburgh Dietetic Association, and was elected Pennsylvania delegate to and appointed chair of the Advisory Committee of the ADA’s Food and Nutrition Conference and Exhibition in 2002. The Pennsylvania Dietetic Association presented her with the Keystone Award in 1998 and the Outstanding Dietitian of Pennsylvania Award in 2002.
Steven Mister is president and CEO of the Council for Responsible Nutrition (CRN), the leading trade association representing product manufacturers and raw ingredient suppliers of dietary supplements. He holds a B.S. from Towson University, an M.A. in political communication from the University of Maryland, and a law degree from the College of William and Mary. Before joining CRN in 2005 he was director of government affairs at the National Association of Professional Employer Organizations. Previously Mister served in several roles for over a decade at the Consumer Healthcare Products Association (CHPA), most recently as vice president and associate general counsel with responsibility for CHPA’s state government relations program. He also worked as an attorney in the Washington, D.C., law firm of Wiley, Rein & Fielding in general litigation, government ethics, and federal election law practice groups, and had a stint on Capitol Hill as a media relations assistant for former U.S. Senator Charles McMathias, Jr.

Robert H. O’Holla is vice president of Regulatory Affairs—Medical Devices and Diagnostics Group for Johnson & Johnson. He holds a bachelor’s degree in biology from Upsala College and an M.B.A. in general management from Fairleigh Dickinson University. During his career he has held both regulatory and quality assurance positions with manufacturers of medical equipment, implants, and sterile disposables. O’Holla is very active with AdvaMed in the areas of product approval and FDA legislation, including the Medical Device User Fee and Modernization Act. AdvaMed recently honored him as an “AdvaMed Achiever” in recognition of his outstanding contributions to the work of AdvaMed and on behalf of the industry. In 2002 O’Holla was awarded the Richard E. Greco Award, the highest honor bestowed by the Regulatory Affairs Professionals Society (RAPS). The award recognizes outstanding leaders who have made significant contributions to the regulatory affairs profession and to RAPS and who show
personal involvement and commitment in their personal lives. He is currently president of RAPS and a member of the Food and Drug Law Institute Medical Devices Committee.

Barbara O. Schneeman is the director of the FDA Office of Nutritional Products, Labeling, and Dietary Supplements in the Center for Food Safety and Applied Nutrition (CFSAN). Schneeman received her B.S. from the University of California, Davis, in food science and technology and her Ph.D. in nutrition from the University of California, Berkeley. She oversees the development of policy and regulations for dietary supplements, nutrition labeling and food standards, infant formula, and medical foods. Prior to joining the FDA she served as a member of the faculty and administration at the University of California, Davis, where she held appointments in the departments of nutrition, food science and technology, and internal medicine in the School of Medicine. Schneeman has served as assistant administrator for nutrition in the Agricultural Research Service in the U.S. Department of Agriculture.

Daniel Schultz is the director of the FDA Center for Devices and Radiological Health. Schultz holds a B.A. in political science from the City College of New York and received his M.D. from the University of Pittsburgh. He is board certified in general surgery and family practice. Schultz entered the Commissioned Corps of the U.S. Public Health Service in 1974, where he served in the PHS Indian Health Service as a hospital clinical director and a surgical resident. In 1983 he was appointed chief of surgery at the Indian Health Hospital in Santa Fe, New Mexico, a post he held for eleven years. In 1994 Schultz joined the Center for Devices and Radiological Health of the FDA, where he served in CDRH’s Office of Device Evaluation, first as a medical officer, then a division director, then the office’s deputy director; in 2004 he was appointed its director.
Andrew C. von Eschenbach is the twentieth commissioner of the FDA. From 2002 to 2006 he served as the director of the National Cancer Institute (NCI). He earned a B.S. from St. Joseph’s University and an M.D. from Georgetown University. He completed his internship at Philadelphia General Hospital and his residency in urologic surgery at Pennsylvania Hospital in Philadelphia and then was an instructor in urology at the University of Pennsylvania School of Medicine. Before his appointment as director of NCI, von Eschenbach spent twenty-five years at the University of Texas M. D. Anderson Cancer Center in Houston, ultimately serving as executive vice president and chief academic officer. In that position he led a faculty of more than a thousand cancer researchers and clinicians. In 2006 *Time* magazine chose von Eschenbach as one of the one hundred most influential people to shape the world. He has made significant contributions to scientific literature, authoring more than two hundred articles, books, and book chapters. He has also served as an editorial board member for several leading journals and on several organizational boards.

**About the Editors**

Arthur Daemmrich is an assistant professor in business, government, and international economy at Harvard Business School, where his research and teaching focus on health care and business in regulated environments. Daemmrich was previously the director of the Center for Contemporary History and Policy at the Chemical Heritage Foundation. He received his B.A. from the University of Pennsylvania and a Ph.D. in science and technology studies from Cornell University. He has held fellowships from the Social Science Research Council/Berlin Program for Advanced German and European Studies, the Kennedy School of Government at Harvard University, and the Chemical Heritage Foundation. He has published widely on biotechnology
policy and politics, the sociology of medicine, and pharmaceutical drug regulation.

Joanna Radin holds an M.A. in the history and sociology of science from the University of Pennsylvania, where she is pursuing a Ph.D. She is also a research associate at the Chemical Heritage Foundation. She earned B.S. and M.S. degrees in communications from Cornell University and has consulted as a risk communications specialist to leading public health and environmental management organizations.