DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 185

The Pharmaceutical Regulatory Process

Second Edition

edited by

Ira R. Berry
Robert P. Martin

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The Pharmaceutical Regulatory Process

DRUGS AND THE PHARMACEUTICAL SCIENCES

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edited by

Ira R. Berry

International Regulatory Business Consultants, LLC
Freehold, New Jersey, USA

Robert P. Martin

RPMartin Consulting
Lebanon, Pennsylvania, USA.

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Preface

This book is a follow-up to the First Edition that described the regulatory process by which sponsors of pharmaceutical products receive approval to market—especially for the U.S. market and through the approval by the U.S. Food and Drug Administration (FDA). The First Edition provided a history of pharmaceutical regulations, policies, and guidances. This Second Edition, now several years later, describes the many changes that have taken place such that terminology is different, updated requirements are based on stricter scientific standards and with some product registrations and industry practices facing basic changes in a constantly changing regulatory environment. This Second Edition contains the subject matter from the First Edition, but with in-depth, updated, and reformed requirements. New additions cover the need for established drug safety standards for post-approval marketed products, marketing drugs that have not required regulatory approval, and the increased supply of APIs and drug products from foreign countries. Just as for the First Edition, this Second Edition is intended to provide an understanding of the requirements to obtain regulatory approval to market a pharmaceutical product and also the policies and procedures needed by pharmaceutical companies to create and implement regulatory compliance postapproval. This book provides the most current information available from industry professionals, practicing attorneys, and FDA regulators—to be used by students, industry professionals, and any person needing to understand the mechanisms and means to establish regulatory compliance for pharmaceutical products and company practices.

The first section of the book includes chapters that describe the legal requirements needed to obtain regulatory approval of pharmaceutical products and remain in regulatory compliance. The first chapter describes the history, "Pharmaceutical Regulations Before and After the Food, Drug, and Cosmetic Act." From the drug approval system that was revised in 1984 and updated in the 1990s, there have been significant changes in order to create a more reasonable and practical regulatory scheme. The chapter "Modernizing the Food and Drug Administration" reviews the substantive legal changes that have been made to FDA and the regulatory process. "The New Drug Approval Process—Before and After 1962" chapter contains the basic requirements for a sponsor to obtain approval of a New Drug. The next chapter focuses on the "Generic Drug Approval Process: Hatch-Waxman Update." The importance of generic drugs to reduce health-care costs is ever more important and this chapter is focused on these issues. The regulation of biological products and the debate regarding creation of a legislative scheme for "follow-on biologics" continue to present many medical, scientific, and regulatory issues that are covered in the chapter "FDA Regulation of Biological Products." The next chapter, "FDA's Antibiotic Regulatory Scheme: Then and Now," addresses the current requirements for

regulatory approval of an antibiotic product. The chapter "Generic Drugs in a Changing Intellectual Property Landscape" describes current patent issues relating to the relationship between New Drugs and Generic Drugs. "The Influence of the Prescription Drug User Fee Act on the Approval Process" chapter has been updated with major legislative revisions that impact the requirements for drug safety reviews, product regulatory approvals, and marketing practices. The next chapter, "Clinical Research Requirements for New Drug Applications," provides an update to the clinical testing requirements for pharmaceutical products. "The Post-Approval Marketing Practices Regarding Drug Safety and Pharmacovigilance" the chapter describes the requirement for a pharmacovigilance program that should be designed to document and prevent widespread safety issues related to a pharmaceutical product postapproval. The next chapter describes the history and current programs for "Drugs Marketed Without FDA Approval." Approval from FDA is not required prior to marketing all pharmaceutical products; however, this issue has been receiving a good amount of attention from FDA—and industry has been focused on working with FDA to keep these products in regulatory compliance following current standards. The issues are complex and the chapter provides an excellent review and explanation. The chapter "FDA Regulation of Foreign Drug Imports, the Need for Improvement" follows and describes the current problems and issues that have arisen from the expanded scope of the importation of pharmaceuticals from foreign countries.

The second section of the book deals with updated specific regulatory requirements for product applications for approval and also postmarketing practices. The first chapter describes the role of "Active Pharmaceutical Ingredients" in regulatory approval of a drug product. It is common for an API to be produced by a different manufacturer from the dosage form manufacturer such that the regulatory requirements must be clear. The next three chapters describe the industry's current views for "Obtaining Approval of NDAs and ANDAs from a Chemistry, Manufacturing and Controls Perspective," "Obtaining Approval of a Generic Drug: Pre-1984 to the Present," and "New Developments in the Approval and Marketing of Nonprescription or OTC Drugs." Emphasis is given to the Common Technical Document format. Along with these three chapters, the next chapter should be followed alongside—"Current Good Manufacturing Practice and the Drug Approval Process," which is a critical part of the process for pharmaceutical product regulatory approvals. The next chapter, "The Influence of the USP on the Drug Approval Process," continues to be necessary for registration of pharmaceuticals as compliance with this compendium on pharmaceutical standards is required. The chapter "Ways, Means and Evolving Trends in the U.S. Registration of Drug Products from Foreign Countries" describes current issues related to the registration and marketing of drugs produced in foreign countries such as drug safety, the critical path to develop new drugs, and evidence needed to establish efficacy. The chapter "Impact of Government Regulation on Prescription Drug Marketing and Promotion" addresses the continually increased depth and enforcement taken by FDA in marketing and advertising practices. The next chapter addresses "CMC Post-Approval Regulatory Affairs: Constantly Managing Change." This continues to be a critically important practice that needs to be followed postapproval so that change for improvement can be implemented. The last chapter, "Living with 21 CFR Part 11 Compliance," covers the significant changes that have occurred for electronic documentation, with a discussion of computer validation.

This Second Edition provides an update to the significant changes that have occurred in the regulation of pharmaceutical products since the First Edition was published. These changes have made the First Edition a basic history book in government regulations and requirements in many respects. This new edition provides invaluable information—just as the First Edition—to the newcomer working in the pharmaceutical industry as well as to students. The world of regulations for the pharmaceutical industry is constantly changing—the basics remain the same as a foundation—but the science, interpretation, and implementation expand as technology increases.

Ira R. Berry
Robert P. Martin

Contents

Contributors

Lorien Armour Armour CMC Regulatory Consulting, LLC, Durham, North Carolina, U.S.A.

Jane Baluss Foley & Lardner LLP, Washington, D.C., U.S.A.

Ann M. Begley, Esq. K. & L. Gates LLP, Washington, D.C., U.S.A.

Ira R. Berry International Regulatory Business Consultants, LLC, Freehold, New Jersey, U.S.A.

Marie C. Boyd Covington & Burling LLP, Washington, D.C., U.S.A.

Paul A. Braier, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

Richard L. Burcham BPI Technologies, Corp., Irving, Texas, U.S.A.

Krista Hessler Carver Covington & Burling LLP, Washington, D.C., U.S.A.

Edward M. Cohen EMC Consulting Services, Newtown, Connecticut, U.S.A.

Benjamin L. England Benjamin L. England & Associates, LLC, FDAImports.com, Inc., Columbia, Maryland, U.S.A.

Michael J. Fink, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

Loren Gelber RRI Consulting Inc., Lake Wylie, South Carolina, U.S.A.

Daniel Glassman Medimetriks Pharmaceuticals, Inc., Fairfield, New Jersey, U.S.A.

Gene Goldberg Medimetriks Pharmaceuticals, Inc., Fairfield, New Jersey, U.S.A.

Neil F. Greenblum, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

Alberto Grignolo PAREXEL International Corporation, Waltham, Massachusetts, U.S.A.

Marc S. Gross Darby & Darby, P.C., New York, New York, U.S.A.

Michael S. Labson Covington & Burling LLP, Washington, D.C., U.S.A.

Max S. Lazar FDA Regulatory Compliance Consulting, Surprise, Arizona, U.S.A.

Jay Lessler Darby & Darby, P.C., New York, New York, U.S.A.

Leo J. Lucisano GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.

S. Peter Ludwig Darby & Darby, P.C., New York, New York, U.S.A.

Robert P. Martin RP Martin Consulting, Lebanon, P.A., U.S.A.

William J. Mead Consultant, Rowayton, Connecticut, U.S.A.

Kevin A. Miller GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.

Sean Myers-Payne, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

P. Branko Pejic, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

Michael P. Peskoe Edwards Angell Palmer & Dodge LLP, Boston, Massachusetts, U.S.A.

David Rosen Foley & Lardner LLP, Washington, D.C., U.S.A.

Stephen M. Roylance, Esq. Greenblum & Bernstein, P.L.C., Reston, Virginia, U.S.A.

Marc J. Scheineson, Esq. Alston & Bird LLP, Washington, D.C., U.S.A.

Dhiren N. Shah Aventis Pharmaceuticals, Kansas City, Missouri, U.S.A.

Barbara Spallitta Reckitt Benckiser, Inc., Parsippany, New Jersey, U.S.A.

John P. Swann FDA History Office, Rockville, Maryland, U.S.A.

Arthur Y. Tsien, Esq. Olsson Frank Weeda Terman Bode Matz PC, Washington, D.C., U.S.A.

Amanda L. Vaught Darby & Darby, P.C., New York, New York, U.S.A.

Irving L. Wiesen, Esq. Law Offices of Irving L. Wiesen, Esq., New York, New York, U.S.A.

Gary L. Yingling, Esq. K. & L. Gates LLP, Washington, D.C., U.S.A.

1 Pharmaceutical Regulation Before and After the Food, Drug, and Cosmetic Act

John P. Swann
FDA History Office, Rockville, Maryland, U.S.A.

INTRODUCTION: 19TH-CENTURY BACKGROUND TO DRUG REGULATION IN THE UNITED STATES

Federal drug regulation in 19th-century America was a fleeting phenomenon, limited in part by a lack of both scientific capacity and sustained political exigency. Citizens stood a better chance of being safeguarded by their own states, although the legislation and enforcement varied widely in this period. By the turn of the 20th century, Connecticut, Georgia, Illinois, Iowa, the Oklahoma territory, California, and most other states had outlawed drug adulteration and/or failure to label a medicine that had morphine, cocaine, digitalis, nux vomica, chloroform, cantharides, strychnine, ergot, or a host of other substances (1,2). Typically, violations were considered as misdemeanors and were penalized accordingly. But absent a federal proscription, it was all the protection a citizen might hope for.

Still, there were some notable though short-lived developments at the national level. Baltimore physician James Smith, inspired by the marketing of spurious smallpox vaccine, convinced Congress to pass a law in 1813 to ensure the provision of reliable vaccine. Under this law, the president appointed a so-called vaccine agent (Smith) "to preserve the genuine vaccine matter, and to furnish the same to any citizen of the United States, whenever it may be applied for, through the medium of the post office." The blame for a smallpox outbreak in North Carolina in 1822 was assigned to vaccine supplied by the vaccine agent, although this was never proven. The impact of the event led to repeal of the vaccine act and restoration to states of the responsibility for pure and effective smallpox vaccine (3).

The publication of the *The Pharmacopeia of the United States of America* in 1820 was a milestone in the history of drug regulation because it established a national compendium of drug standards to help respond to what medical and pharmaceutical professionals observed to be an increasingly corrupt drug supply. Ultimately, it would prove to be unique among most legally recognized publications of this kind in the world because it was, and still is, a private venture. There had been occasional local compilations of standard drugs and their preparation, the first of which was the *Lititz Pharmacopeia* of 1778. But the convention that assumed responsibility for a national collection of drug standards and their preparation had something broader in mind.

Led by New Hampshire native Lyman Spalding, 11 physician delegates from medical societies and schools across the country, representing four districts, met in Washington in January 1820 to discuss drafts and recommendations from district proceedings and what would and would not be included in the USP. The first USP aimed "to select from among substances which possess medical power, those, the utility of which is most fully established and best understood; and to form from

them preparations and compositions, in which their powers may be exerted to the greatest advantage" (4). The USP thus endeavored to elevate the pharmaceutical armamentarium in a way that would make both the practice of medicine and the practice of pharmacy more reliable (5–8).

The first federal law that addressed pharmaceuticals in general invoked the USP as well as other pharmacopeias. Lewis Caleb Beck's 1846 publication, *Adulteration of Various Substances Used in Medicine and the Arts, with the Means of Detecting Them: Intended as a Manual for the Physician, the Apothecary, and the Artisan*, revealed an American marketplace rife with adulterated medicines. Opium, one of the most valued medicines, was most frequently subjected to fraud, mixed with all manner of deceptive ingredients, such as gum arabic, sand, and lead. Beck identified many other drugs commonly adulterated, including tartar emetic, quinine, and rhubarb. It was a state of affairs perhaps best captured by British statesman and pharmacist Jacob Bell, who related the widespread belief abroad that drugs rendered unsuitable by decay or fraud were still "good enough for America" (9).

If Beck's book provided the scientific evidence why the United States needed a law to protect the drug supply, then the Mexican–American War (1846–1848) provided the political impetus. Many in Congress blamed adulterated drugs for the massive wartime deaths. In truth, considering the drugs then available, it would have made little difference whether or not the drugs were pure. Squalid camps, inadequate nutrition, and an understaffed medical corps were largely responsible for deaths due to disease—about 10% of the total fighting force each year, a rate seven times the mortality rate due to combat (10). The continuing prevalence of drug adulteration in the 1840s, particularly evident in the ports, produced, as James Harvey Young observed, "a sense of outrage." Senator John Davis of Massachusetts believed that, "If we can stop the importation of the spurious drug from abroad, we shall know how to deal with those who may choose to go into their adulteration in the United States" (11). Such sentiments, combined with Congress's conception of pharmaceutical fraud in the Mexican–American conflict and the documentation supplied by Beck, helped shape a law that attempted to bring some order to the chaos.

The Drug Import Law, signed by President James K. Polk on June 26, 1848, required the examination of all drugs that came into the ports of New York, Boston, Philadelphia, Baltimore, Charleston, and New Orleans for "quality, purity, and fitness for medical purposes." The law identified the USP as well as the pharmacopeias and dispensatories of Edinburgh, London, France, and Germany as the source of standards used by the port examiners in their appraisals. Drugs had to be labeled with the name of the manufacturer and the place of preparation. The Secretary of the Treasury was authorized to appoint suitably qualified personnel at each of these ports. Any drug so adulterated or deteriorated to fall short of the standard of purity or strength as established by these compendia would not pass the customhouse. The owner or consignee could request a reexamination by an analytical chemist endorsed by the medical profession and the local school of medicine or pharmacy. But if that analysis upheld the port examiner, the violative drug would be either removed by the owner or destroyed by the port (12).

Initially, the law was enforced vigorously by those appointed by Secretary of the Treasury Robert J. Walker. In the first few months, the New York port was reported to have turned away over 90,000 pounds of drugs. Some even hoped, like

Senator Davis, that it might be possible to address the problem of domestic traffic in problematical drugs. However, the impact of the law soon diminished. In part, this was due to inadequately developed methods of analysis, a problem that pharmacists, in particular, tried to rectify. But the problem also rested in the appointment of unqualified individuals to special examiner positions, appointments which began to be awarded more on the basis of political debts than the suitable qualifications as stated in the law. By 1860, Edward Squibb announced that the law was barely enforced any more, and that remained the case despite the efforts of some physicians and pharmacists for the remainder of the century (13–15).

EARLY REGULATION OF BIOLOGICAL THERAPIES

The next significant milestone in the history of regulating therapeutic products in the United States followed a major advancement in biological therapeutics. In 1890, Emil von Behring and Shibasaburo Kitasato, working at the Robert Koch Institute in Berlin, announced that they had successfully treated diphtheria by injecting patients with blood serum of animals immunized against the pathogen. The last two decades of the 19th century witnessed the identification of nearly two dozen microorganisms responsible for disease, and the work of von Behring, Kitasato, Louis Pasteur, Emile Roux, and others applied these discoveries to develop and refine biological treatments for these diseases (16,17).

State and local public health laboratories and a few commercial concerns soon began producing their own diphtheria antitoxin once European scientists perfected the production methodology. On the eve of this milieu, Joseph Kinyoun, head of the Hygienic Laboratory of the U.S. Marine Hospital Service (later renamed the Public Health Service), warned the Surgeon General in November 1894 of "... what will evidently ensue in our country. Many persons will, during the ensuing year, commence to prepare the (antidiphtheria) serum as a business enterprise, and there will, without a doubt, be many worthless articles called antitoxin thrown upon the market. All the serum intended for sale should be made or tested by competent persons. The testing, in fact, should be done by disinterested parties. The danger with us is perhaps greater than could exist here (in Germany) under any circumstances" (18). Early in 1895, the Hygienic Laboratory developed a standard diphtheria antitoxin for distribution (19–21). Businesses, as Kinyoun suspected, indeed took up production, but it was the antitoxin manufactured by a municipal public health laboratory that launched a movement for regulatory intervention (Fig. 1).

In October 1901, the St. Louis Health Department produced a batch of antitoxin that killed 13 children being treated for diphtheria; the cause of death in each case was tetanus. An investigation led by the city council and the health department revealed that the consulting bacteriologist who had produced the antitoxin had used a horse that contracted and later died of tetanus. The bacteriologist allegedly was aware of the horse's condition but failed to destroy the product or otherwise prevent its distribution. Although he was unaware of the tainted source of the antitoxin, the janitor in the laboratory had responsibility for bottling the product; he complicated recovery of the antitoxin by initially claiming that the antitoxin had been destroyed. The incident in St. Louis was not an isolated one. There were other accidents also involving biological medicines, such as about 100 cases of postvaccination tetanus that occurred in Camden, New Jersey, in the Fall of 1901, where nine children died.

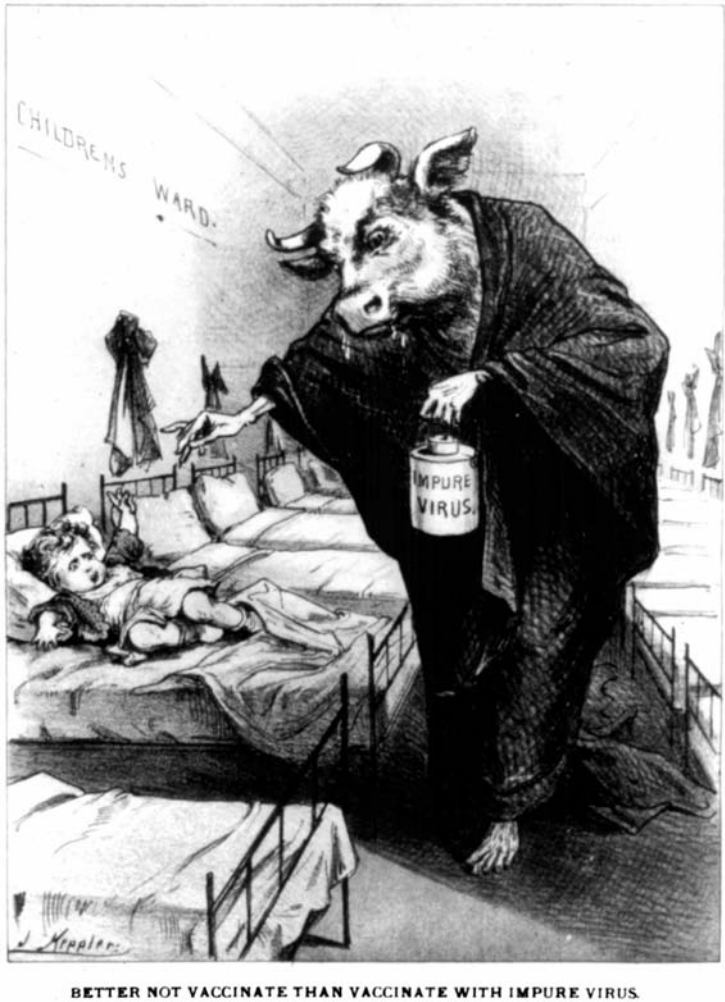

FIGURE 1 This cartoon from *Puck*, 1880, deftly captures the fear of vaccination with unreliable vaccine matter. *Source*: Courtesy of William Helfand.

But it was the St. Louis disaster that was specifically invoked (22) in the hearings on a bill that proposed bringing production of biologics under federal control. Introduced on April 5, 1902, President Theodore Roosevelt signed the Biologics Control Act on July 1, 1902, virtual light speed compared to the quarter-century it took for the admittedly more comprehensive and much more hotly contested Food and Drugs Act of 1906 (23). The Hygienic Laboratory was responsible for enforcement of the 1902 legislation.

Drawing upon extant legislation in Europe, this law required manufacturers of any biological medicine or analogous product to be licensed annually by the government, and licensure was predicated on a satisfactory and unannounced

inspection of the establishment. All aspects of production could be examined, including records. Samples of licensed products were obtained on the open market and tested at the Hygienic Laboratory for purity and potency. Licenses could be suspended pending correction of a manufacturing or product defect, and violation of the law was subject to a fine of up to $500 and/or imprisonment for up to 1 year. While there certainly were cases of license suspensions, there appears to be little evidence that the Hygienic Laboratory pursued fines or imprisonment under the law until the early 1960s (24–26). The number of licenses issued by the Hygienic Laboratory grew quickly, from 13 concerns licensed to produce mostly diphtheria antitoxin and smallpox vaccine in 1904, to two dozen operations producing about 20 different medicines in 1908, to 41 establishments licensed for over 100 biologics in 1921 (27–30).

FEDERAL AND PRIVATE REGULATION OF DRUGS IN THE EARLY 20TH CENTURY

Other federal agencies offered limited regulation over pharmaceuticals beginning in the early 20th century. The Post Office Department, for example, was able to prosecute some products that were otherwise beyond the reach of the government under the postal fraud laws of 1872 and 1895 (31,32). These laws prohibited the use of mail to collect money under fraudulent pretenses. Violations resulted in a fraud order, wherein the offending mail was intercepted and returned to the sender. Thus in 1928 the Post Office secured a fraud order, upheld on appeal, against Tuberclecide, a worthless treatment for tuberculosis, and years earlier against Habitina, an alleged drug addiction cure that contained both morphine and heroin (33,34). The Federal Trade Commission (FTC) exercised its jurisdiction over drug advertising from time to time following its establishment in 1914. For example, it attempted to regulate Marmola, a hazardous thyroid preparation intended for weight reduction, on two occasions in the 1920s and 1930s (35). The Wheeler-Lea Amendment of 1938 clarified FTC's unique authority over all drug advertising, although jurisdiction over prescription drug advertising was transferred to the U.S. Food and Drug Administration (FDA) in 1962 (36–38).

Ironically, probably the most significant effort to regulate prescription drugs prior to 1938 was a private venture that was voluntary, under the American Medical Association (AMA). Shortly after the turn of the century, the AMA and the American Pharmaceutical Association (APA) combined resources to press for the establishment of a federal authority that would certify drugs—and thus help rid the landscape of patent medicines. These not only posed a threat to the public health but they also represented some competition for physicians. Nostrums certainly played an important role in the retail business of many pharmacists, but others in the profession excoriated their sale. The AMA abandoned the idea of federal certification and instead formed its own Council on Pharmacy and Chemistry in 1905, a 15-member group that included physicians, pharmacists, pharmacologists, chemists, and government representatives. The AMA Board of Trustees charged the council to publish an annual volume of proprietary pharmaceuticals approved by the council that were not, according to pharmacopeial rules, permitted in the USP (39–41).

Manufacturers submitted to the council evidence to support any claims made for the drug and a proposed name, and the council relied heavily on the advice of outside consultants to evaluate these data. An accepted drug would be included

in its compendium, *New and Nonofficial Remedies* (NNR), which entitled the firm to label its drug with the council's "accepted" seal. But under the council's rules, no pharmaceutical would be admitted to NNR if it had "unwarranted, exaggerated or misleading statements as to therapeutic value." Moreover, a drug would not be accepted if its firm derived substantial earnings from products not listed in NNR. But rejection by the council meant more than just failure to appear in NNR or enhance its label. Unaccepted drugs were denied the right to advertise in the family of AMA journals (42–45).

The council terminated its acceptance program in 1955, largely due to the AMA's depletion of cash reserves and a growing apathy for the program within the association, according to one informed observer (46). However, the council continued to publish its compendium of drugs for reference use of the profession. With the proscriptive element of the program inactivated, the possibility existed in which a drug might be advertised in the *Journal of the American Medical Association* (*JAMA*) for an indication not supported in NNR (47). Moreover, firms were less compelled to submit the sort of evidence to the council that they had in the past, such that the council's consultants had to search for supplemental data on NNR candidates elsewhere. Still, NNR included comparative assessments of a drug's efficacy, something FDA did not do when the efficacy statutes were passed (48–50).

THE DRUG MARKETPLACE AT THE TURN OF THE CENTURY

Federal regulation over the bulk of the drug supply was still nonexistent at the turn of the 20th century. It was a menacing marketplace. Despite the existence of several comprehensive drug compendia—including the USP—there were no legally required standards of identity for drugs, whether the pharmaceuticals were prescribed by a physician and dispensed by a pharmacist (so-called ethical drugs) or purchased directly by the consumer for self-medication. Some of the manufacturers of the former by this time had quality-control procedures in place and produced standardized drugs of predictable therapeutic response. Parke-Davis was the first firm to subscribe to this approach, introducing 20 chemically assayed fluidextracts of botanicals by 1883 (51,52). Parke-Davis and Mulford were the early leaders in the production of biologicals, a venture that by definition and by law required the institutionalization of science. Incorporating science was, as Jonathan Liebenau points out, good business for drug manufacturers even at this early stage. And they made sure their clientele knew it (53).

But science was still very much in its infancy for most of the American pharmaceutical industry at the turn of the century. It was an expensive proposition, and many company chiefs remained to be convinced that more (or any) science and research necessarily meant more business (54). To be sure, even the ethical industry had its share of scientifically questionable products. One of Eli Lilly and Company's best sellers at this time was Succus Alterans, a blood purifier and treatment for rheumatism, syphilis, and a variety of skin diseases that Lilly supposedly derived from a Creek Indian remedy (55). In 1889, Smith Kline & French purchased the D. B. Hand Company and then manufactured and distributed the Hand line of products, still under the Hand brand. This inventory consisted of teething lotions, colic cures, croup and cough medicine, worm elixir, and other preparations advertised for infants and children. Like so many other pediatric products of other firms

FIGURE 2 Hunt's Remedy, manufactured since 1850, illustrates the unrestricted claims and eye-catching advertising imagery that characterized many patent medicines at the turn of the 20th century. This particular advertisement was used for the design of a 1998 U.S. postage stamp to commemorate the 1906 Food and Drugs Act.

at this time, these Hand medicines typically contained alcohol, opium, and chloral hydrate (56–58).

But regardless of the extent to which the ethical industry marketed nostrums, it paled next to the patent medicine industry, those who vended William Radam's Microbe Killer, Mrs. Winslow's Soothing Syrup, Swaim's Panacea, Benjamin Bye's Soothing Balmy Oils to cure cancer, Dr. Hollick's Aphrodisiac Remedy, and on and on (59). Nostrums were omnipresent in late 19th-century America, and their rise, not coincidentally, was paralleling that of advertising. Products appealed to exotica, the medical knowledge of Native Americans, death, religion, patriotism, mythology, and eventually new developments in science. Nothing but the size of the bottle prevented patent medicines makers from claiming anything and putting anything in their products (Fig. 2). At the same time, the biomedical sciences awaited elaboration, leaving medicine ill equipped to deal with most diseases. If there were a demand for cancer and arthritis cures, baldness remedies, bust developers, and manhood restorers, a cure could be supplied. And if there were not a demand, that too could be manufactured.

The nostrum industry undoubtedly knew how to market its wares, but companies also promoted their interests in more surreptitious ways. For example, they subdued any curiosity in the press with their economic strength. By the 1890s, patent medicine manufacturers used so-called "red clauses" in their advertising contracts to muzzle newspapers and magazines. The contracts would be voided if a state law regulating nostrums were passed. Thus, not only were many editorials silent on the need for such laws, they actively campaigned against them.

THE FEDERAL FOOD AND DRUGS ACT OF 1906

Such was the pharmaceutical landscape in America as the 20th century began. A few muckraking journalists helped reveal the red clauses, the false testimonials, the nostrums laden with harmful ingredients, the unfounded cures for cancer, tuberculosis, syphilis, narcotic addiction, and other serious as well as self-limited diseases. The most influential patent medicine exposé was a 10-part series entitled "The Great American Fraud," by Samuel Hopkins Adams, which began in *Collier's* on October 7, 1905, and ended the following February. A subsequent series by Adams examined doctors who advertised fake clinics. That same month saw the publication of another work that, more than any other single event, spurred on passage of a comprehensive federal law. Socialist writer Upton Sinclair published *The Jungle*, a fact-based novel about immigrant life and the meatpacking industry of Chicago. Sinclair's shocking and revolting story was verified by government undercover investigators.

The search for a federal law to correct abuses in the food and drug marketplace began long before Adams and Sinclair initiated their investigations. Congress received the first bill to address these concerns in January 1879, although that version addressed only foods; some months later another bill, this time encompassing drugs as well as foods, was introduced in the House. Every session of Congress for the next 25 years considered at least one sweeping food and drug control bill (60). Those who believed they would be adversely affected by an omnibus law managed to thwart passage of the dozens of bills that were introduced during this span. But their opponents obviously were equal to the task—or at least persistent.

Many championed a food and drug law, but one person more than any other was responsible for keeping the need for such a law squarely in front of both the Congress and the people. Harvey Washington Wiley was a chemist on the faculty of Purdue University when he came to Washington in 1883 to become the fourth chief chemist in the Department of Agriculture. From the time of his arrival in the capital, Wiley was an enthusiastic, infectious, and effective champion for remedial legislation. When he was not stumping for a law, he was publishing extensively on the proliferation of food adulteration (61). His forceful personality and commitment to reform brought together important but disparate groups to help lobby Capitol Hill, including state food and drug officials, the General Federation of Women's Clubs, the APA, and the AMA (62–64).

On June 30, 1906, President Roosevelt signed the Food and Drugs Act into law (65), nearly 4 years to the day after he signed the Biologics Control Act. The law prohibited interstate commerce in adulterated or misbranded foods and drugs. It was unlawful to add an ingredient to a food that would represent a health hazard, result in a filthy or decomposed product, conceal damage, or substitute for the food itself. If the manufacturer chose to label the weight or measure of the food, that had

to be done accurately. A food or drug label could not be false or misleading in any particular.

A drug under the act was any substance intended for the cure, mitigation, or prevention of disease in humans or animals. It could not be sold in any condition of purity, strength, or quality other than that stated in the USP or the *National Formulary*, unless the specific variation from that standard was stated on the label. The presence and amount of 11 dangerous ingredients, including heroin, morphine, cocaine, and alcohol, had to be labeled on all drugs (and foods). Violative goods were subject to seizure and, if upheld by the court, destruction. Infractions were considered misdemeanors, and those behind the offense could be fined up to $500 and imprisoned for up to one year. The Bureau of Chemistry of the Department of Agriculture, the home of more chemists than anywhere else in the U.S. government (66), was assigned to enforce the law and promulgate regulations (67).

APPLYING THE NEW LAW TO DRUGS

One immediate impact of the law was to persuade many patent medicine manufacturers to remove ingredients from their preparations that were subject to labeling. Therapeutic claims, however, were another story. The Bureau of Chemistry quickly applied the law to products that bore false therapeutic claims, based on a charge of misbranding. About 100 such cases were made in 5 years (68). However, when the bureau tried to move against Dr. Johnson's Mild Combination Treatment for Cancer, the firm prevailed over the bureau in court. The case reached the Supreme Court in 1911, which ruled in a 6–3 decision against the government. The majority believed that the 1906 act pertained only to the identity of ingredients in a product. Moreover, the Court believed that the Bureau of Chemistry was capable of making an informed judgment about a drug's contents, "but hardly so as to medical effects." Finally, based on an earlier case involving the Post Office, the court argued that ideas about therapeutics were still too far ranging to come to definitive conclusions (69).

President William Howard Taft asked Congress to develop a legislative solution for the 150 pending drug misbranding cases, as well as those yet to come. Among these cases, according to the president, were "some of the rankest frauds by which the American people were ever deceived" (70). Congress responded in 1912 with the Sherley Amendment, couched as severely as members believed possible without infringing on expressions of opinion. The new law prohibited statements about a product's ingredients or its curative or therapeutic effect that were false and fraudulent (71,72). However, to establish fraud meant that the bureau of chemistry had to show that the manufacturer knew the product was worthless—that there was intent to defraud the consumer. This proved to be difficult in many cases.

For example, Lee Barlett, a former shirt salesman from Pittsburgh, promoted a medicine called Banbar, an extract of the horsetail weed, as an effective treatment for diabetes. Barlett sold Banbar for $12 a pint, a hefty price in the 1920s, but it allowed diabetics to take their medicine orally rather than administering injections of insulin, which Frederick Banting and his colleagues at the University of Toronto had introduced in 1923. The government took Barlett to court for selling a misbranded drug. Elliott P. Joslin, the internationally recognized authority on diabetes, was the plaintiff's principal witness. On the basis of the 12,000 diabetic patients he saw every year, Joslin testified that insulin—combined with diet and exercise—was

FIGURE 3 Pharmacologists in the Bureau of Chemistry employed biological assays to develop the first reference standards issued to industry to promote compliance with the testing requirements for select pharmaceuticals in USP X (1926).

the only effective treatment for this disease. The defense offered hundreds of testimonial letters on behalf of Banbar. The jury found in favor of the defense, despite the fact that the government presented death certificates—attributed to diabetes—for individuals who had submitted these testimonials (73).

Under Wiley, enforcement of the Food and Drugs Act weighed heavily toward foods. Of the first 1000 actions taken by the bureau up to 1911, fewer than one quarter dealt with drugs. And those drug actions typically addressed patent medicines; as seen earlier, false therapeutic claims were a driving force for action. Official drugs such as belladonna and asafetida were the subjects of fewer than 100 of these actions. Most defendants did not challenge the bureau, but rather paid their fines, adjusted their labeling, and continued to advertise as before, since the latter was beyond the reach of the 1906 law (74).

Carl Alsberg followed Wiley as chief chemist in 1912, and he continued to favor foods. But he also focused more attention on ethical drugs. To address these, the bureau developed new analyses for crude drugs, and by the 1920s bureau scientists pioneered biological assays for ergot, digitalis, and other drugs, which were adopted by the USP (75) (Fig. 3). The bureau also monitored drugs dispensed by pharmacists in the District of Columbia (believing state pharmacy boards were the more appropriate monitor elsewhere) beginning in the 1910s and found substantial deviations from official standards. By the early 1930s, FDA and the APA reached an agreement as to what would be considered reasonable tolerances for dispensed drugs (76).

When Walter Campbell succeeded Alsberg in 1921, he revitalized the drug regulatory effort, beginning with the appointment of George Hoover, a physician and chemist, to head drug regulation. The bureau consequently expanded its interests from crude drugs to tablets, discovering fairly wide variations from official standards. But by this time, when the Republicans came to power and the policy was made to be more cooperative with business, court action began to be superseded by negotiation. Hoover met with the pharmaceutical industry's trade associations, the American Drug Manufacturers Association and the American Pharmaceutical Manufacturers Association, which in turn formed so-called contact committees to investigate the tablet problems in cooperation with the bureau. The committees helped improve tableting technologies and negotiated with the bureau over allowable deviations from the labeled amount of active ingredient. But in the New Deal era, drug regulation took a less collaborative tone with industry (77).

TOWARD THE 1938 FOOD, DRUG, AND COSMETIC ACT

The 1906 act was arguably the pinnacle of Progressive Era legislation, but the difficulty of prosecuting medicines with false therapeutic claims was just one of many shortcomings of the 1906 act. Foods did not have standards, cosmetics and medical devices were unregulated, the penalties imposed by the law were paltry relative to the crime, with the exception of the 11 ingredients there was no required listing of drug ingredients, factory inspections—although interpreted and executed by the bureau as warranted under the law—were not explicitly authorized, and although the law prohibited a food that was made to be unsafe, there was no similar protection for drugs. By the 1920s, and increasing considerably after Franklin Roosevelt became president in 1932, FDA began to publicize rather creatively the more egregious examples of deceptive and hazardous products that were on the market and perfectly within the law, an argument for a new comprehensive law (78). Indeed, shortly after FDR's inauguration, Congress began considering bills that would replace the Food and Drugs Act and plug the holes left in consumer protection legislation (79).

The public's vulnerability became dramatically clear in October 1937. Months after the introduction of the wonder drug sulfanilamide, the S. E. Massengill Company of Bristol, Tennessee, began investigating a liquid dosage form for the drug. Their investigation consisted of finding a solvent in which the drug would dissolve (sulfanilamide was known to be stubbornly insoluble) and flavoring and coloring the preparation so as to be especially useful for children and others not inclined toward tablets. Quality control amounted to little more than an organoleptic appraisal. Harold Watkins, the company chemist, selected diethylene glycol as the vehicle for the sulfa without testing the solvent or even examining the medical literature. Had he at least bothered to look, the latter certainly attested to the glycol's poisonous nature. He did not bother testing it himself, he claimed, because glycols were related to glycerin, which had long been used in medicines. The company thus began shipping its Elixir Sulfanilamide from Tennessee and its Kansas City office in early September.

On October 11, a representative from the Tulsa County Medical Society contacted the AMA to inform them that several deaths in the Oklahoma county appeared to be associated with the Massengill product. The physician wanted to

know what the AMA's Council on Pharmacy and Chemistry could tell them about the preparation. Neither Elixir Sulfanilamide nor any Massengill product had ever been accepted by the Council. The FDA heard about the suspicious deaths 3 days after the AMA from a New York physician with ties to Massengill. FDA learned that the Elixir was involved in all the Tulsa fatalities, at which point the agency dispatched its chief medical officer and one of its finest field investigators to Bristol to investigate. They learned that proprietor Samuel E. Massengill issued an inadequate recall notice and that 240 gallons remained unaccounted for.

FDA dedicated virtually its entire field force to tracking down the remaining product—although forced to rely on a technical error for legal cause. Nothing in the 1906 act prohibited unsafe drugs. Rather, FDA was allowed to seize Elixir Sulfanilamide because it was misbranded; an elixir, by definition, had to employ alcohol, and the Massengill medicine of course had none. Most physicians and pharmacists encountered by FDA investigators during the frantic recovery effort were helpful, but some were uncooperative and even obstructive, no doubt to deflect personal responsibility and liability. Much was recovered from warehouses, pharmacy shelves, and medicine cabinets, but overall, Elixir Sulfanilamide killed at least 107, mostly in the South.

Many were children, such as the 6-year-old girl from Tulsa who perished in this ordeal (Fig. 4). Her mother, Marie Nidiffer, wrote to President Roosevelt on November 9: "Tonight Mr. Roosevelt that little voice is stilled. The first time I ever had occasion to call in a doctor for her and she was given the Elixir of Sulfanilamide. Tonight our little home is bleak and full of despair. . . . Even the memory of her is mixed with sorrow for we can see her little body turning to and fro and hear that little voice screaming with pain and it seems as though it drives me insane. . . . Tonight President Roosevelt as you enjoy your little grandchildren of whom we read about, it is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind. . . ." (80–82).

The bills to correct the gaps in the 1906 act had been delayed and diluted over the previous 5 years. However, the impact of the Elixir Sulfanilamide tragedy was to strengthen the drug provisions of the latest bills and in fact propel passage of the law itself. Roosevelt signed the bill on June 25, 1938 (83). The Food, Drug, and Cosmetic Act brought medical devices and cosmetics under regulation, provided for standards of identity for foods, prohibited once and for all false therapeutic claims on drug labeling, required that drugs be labeled with adequate directions for use, authorized factory inspections (which had been executed anyway under the bureau's interpretation of the old law), instituted court injunctions for violative products, corrected abuses in the quality and packaging of foods, instituted adequate drug manufacturing controls (84), and, most important from the standpoint of the history of drug regulation, mandated that all new drugs had to be shown by the manufacturer to be safe before they could be marketed—the birth of the new drug application (NDA). The premarket provision, inspired by the fear of another Elixir Sulfanilamide disaster, had an immediate impact, with over 6000 new drug applications filed in the first 9 years and 13,000 by 1962 (85).

DRUG REGULATION AND THE POSTWAR CHEMOTHERAPEUTIC REVOLUTION

One early development under the drug provisions of the 1938 act concerned self-medication. The law called for adequate directions for use by the patient, and by

Tulsa Oklahoma
Nov 1, 1937

President Roosevelt
Dear Sir.
Two months ago I was happy and working. Taking care of my two little girls. Joan age six and Joan age nine. Our boy would though the depression was that, we had good health and cared other. Joan thought her mother was right in everything and it would have made your heart feel good last November to have seen her jumping + shouting as we listened to your re election over the radio.
Tonight Mr Roosevelt that little voice is stilled. The first time I ever had occasion to call in a doctor for her and she was given the elixer of Sulfanilamide. Tonight our little home is blank + full of despair All that is left to us is the caring for of that little form. Even the memory of her is mixed with sorrow for we can see her little body turning + [illegible] and it seems as tho it drives me insane. During her nine days of illness as we sat by her bed only once did those little eyes lose their dull and unknowing look from + I begged her to look + know me a smile broke over her face + she laughed aloud until me + so quickly it reminded me to smile + know me again.
Tonight President Roosevelt as you enjoy your little grand children of whom we read about, it is my plea that you will take steps to prevent such sales of drugs that will take little lives + leave such suffering behind and such a blank outlook on the future as I have tonight.

FIGURE 4 The face of a drug disaster. This excerpt from a moving letter to President Roosevelt from Mrs. J. Nidiffer of Tulsa describes her anguish and helplessness over the loss of her 6-year-old daughter, Joan Marlar. Ironically, sulfanilamide saved the life of FDR's son just 1 year earlier, not long after American clinicians got their hands on the drug.

1940 FDA issued nearly 30 detailed warning statements to be labeled on a variety of drugs. For example, bromides were labeled with the following: "Warning: Frequent or continued use may lead to mental derangement, skin eruptions or other serious effects. Do not take more than the dosage recommended. Not to be taken by those suffering from kidney disease" (86).

However, it was FDA's opinion within weeks of the law that some drugs simply could not be labeled with adequate directions. For example, the use of a sulfa drug in a venereal disease was hardly routine, complicated as it was by both the adverse reactions that many of the early sulfas produced and the identification and progress of the disease. In other words, FDA ruled that in some cases medical expertise had to be involved in the medication process for the drug to be safe. The agency identified an increasing number of drugs that had to be labeled for dispensing only on the order of a physician or dentist; the birth of another standard of modern medicine, the prescription drug (87–90). This created confusion about how a drug would be categorized—prescription or nonprescription—and who would have primary responsibility for that designation. The absence of statutory direction was resolved in 1951 when the Durham–Humphrey Amendment was passed. That law established broad parameters for deciding which drugs merited designation as prescription legend status and which could be available over the counter (91).

The illegal sale of two groups of prescription drugs, amphetamines and barbiturates, took up more of FDA's drug enforcement time in the 1940s, 1950s, and 1960s than all other drug violations under the 1938 act combined. At first the agency focused on pharmacies, some of which were either selling these drugs over the counter without a prescription or incessantly refilling old prescriptions that did not authorize any refills. By the mid-1950s, FDA's attention turned to the trucking industry, a major source of traffic in these pharmaceuticals, where some spectacular and highly publicized highway crashes were directly connected to the use of amphetamines and barbiturates (92). Eventually many other drugs prone to abuse, such as hallucinogens, were consolidated for special interdiction by FDA under the Drug Abuse Control Amendments of 1965 (93,94). However, 3 years later that function was transferred to what would become the Drug Enforcement Administration (DEA).

The introduction of the sulfa drugs, beginning with sulfanilamide in 1935, launched a revolution in chemotherapy. Statutes and regulations did their best to keep track of new therapies. For example, literally hours before expiration of the patent on insulin (and the University of Toronto's oversight of quality control in the production of the hormone) in 1941, Congress passed the Insulin Amendment to require FDA to test every batch of insulin produced for strength, quality, and purity to ensure its safety and effectiveness (95). A similar law in 1945 provided for FDA certification of batches of penicillin—a service carried out by FDA beginning in 1943 for the War Production Board's supply of penicillin headed for troops. As additional antibiotics were discovered, laws were passed to accommodate them (96–98).

As mentioned earlier, companies flooded FDA with drug applications at the outset. The agency received an average of over 100 NDAs monthly from 1938 to 1941 because sponsors were apparently unsure of what constituted a new drug. NDA 1596, received on August 30, 1939 and approved on September 20, 1939, was for 4-H Household Cough Syrup, consisting of horehound, molasses, and vinegar. The Aiellos Ped-Vale Company submitted NDA 407 on January 12, 1939, for Aiellos Foot Remedy Powder, made up solely of boric acid; FDA approved the application on April 1 of that year. During this period, seven firms and one physician submitted NDAs for aspirin that were approved by FDA. Interestingly, in January 1945 the agency ruled that the indications for aspirin were so well known to consumers that directions for use were not required. Aspirin lollipops, though, were a different matter, requiring a physician's prescription (99–102).

The application submission rate slowed during World War II and the early postwar years to about 350 annually. However, it picked up again in the 1950s to approximately 400 each year, when research funds flooded laboratories almost as fast as pathbreaking new medicines flooded the marketplace. Upon the end of hostilities in Europe, the Committee on Medical Research of the Office of Scientific Research and Development disbursed remaining wartime research funds to the National Institutes of Health (NIH). This source of funding, together with strong congressional support, launched in full force the modern era of autonomously peer-reviewed extramural funding of biomedical research at NIH (103).

In addition, the pharmaceutical industry accelerated a trend that began in the period between the wars, pouring more and more revenue into research and development (104,105). That decision might have been made a little easier by the success of their wartime experience with penicillin, synthetic anti-infective agents, and other drugs. Thus, a host of antibiotics, diuretics, ataractics, corticosteroids, antispasmodics, and other classes of drugs proliferated during that decade (106,107). Of course, the number of supplements grew as the base number of NDAs increased. And then there were some drugs that yielded scores or even hundreds of NDAs, such as diethylstilbestrol and rauwolfia serpentina. David Cavers reports that the latter led to applications from 319 different firms and was included in 2500 different medicines (108).

COMING TO GRIPS WITH EFFICACY BEFORE 1962

Another drug regulation policy was growing increasingly important in the 1950s—the relationship between drug safety and drug efficacy. The idea of federally mandated effectiveness in medicines was nothing new at this time. For example, regulations issued by the National Institutes of Health (formerly the Hygienic Laboratory) in 1934 required that biologics had to work: "[A] license for new products shall not be granted without satisfactory evidence of therapeutic or prophylactic efficiency" (109). This formalized a policy that had been in place for years.

In the late 1930s, FDA promulgated a rule requiring manufacturers of oral or otherwise inert ovary, suprarenal, pituitary, prostate, pineal, and mammary extracts to label their products with a statement that such an article "does not contain any known therapeutically useful constituent of the glands mentioned." Of course, even under the 1906 act, actions taken against patent medicines that made false therapeutic claims were implicitly driven by efficacy considerations (considerations that the Supreme Court believed were ahead of their time). The Insulin Amendment, Penicillin Amendment, and the other antibiotic amendments literally invoked efficacy as a prerequisite for certification by FDA. Reviews of certain NDAs that claimed to treat serious diseases such as pneumonia certainly took efficacy into account (110). The concept that in certain cases a drug could not be safe without being effective was employed but never pressed forward as an official policy—until Hepasyn® came along.

The Hepasyn story began in the early 1930s, when various researchers observed that cancerous tissue bore a high concentration of the amino acid, arginine, which appeared to promote cell division in tumors. Some tried to exploit this observation by applying the liver enzyme arginase, which helps to hydrolyze arginine, as a possible treatment to control tumor growth. Success was fleeting for most. However, dentist Wesley G. Irons, working as an anatomist at the Schools of

Pharmacy and Dentistry at the University of California at San Francisco in the 1940s, claimed to have success treating animal tumors with arginase. When his funding fell through at the university, Irons was offered funding and laboratory space at the San Francisco College of Mortuary Science, a source for cadavers in Irons's classes.

The mortuary school reserved commercial rights to Irons's work and served as the manufacturing establishment for Hepasyn, the name they gave to arginase. In November 1950, the school arranged with a Hollywood clinician to test arginase, and within a year 100 patients had received the substance. Eventually, the Hollywood physician began treating other cancer patients on an ambulatory basis once a week at the mortuary school. The story became even more curious after Irons and the school parted company, but the San Francisco school submitted an NDA late in 1953. FDA inspectors visited the mortuary school and found serious production problems, such as organoleptic sterility testing. The NDA contained results for only 10 patients, although the sponsors claimed to have data on 175 patients. FDA, not surprisingly, considered the application incomplete and requested more data. As problematical as the manufacturing operation was, FDA chose to focus on the clinical evidence submitted by the college (Fig. 5).

By October 1955, the application was deemed complete enough for a review. The agency's strategy was made clear to a medical officer in San Francisco: "We have given considerable thought to the proper handling of this application and have decided in conjunction with (General Counsel William) Goodrich that since this preparation is ineffective in the treatment of malignant disease its use is not safe in such situations. In other words, while section 505 does not refer to efficacy we are going to try and take the position that efficacy is so intimately bound up in the use of this material that the lack of efficacy will make it unsafe for use" (111). The Hepasyn review thus was not going to be just another NDA evaluation. Rather, it was to be a blatant stand on therapeutics and the law. FDA's expectation or hope was that the San Francisco College of Mortuary Science, its application denied on the basis of lack of efficacy, would appeal the decision in an administrative hearing.

In late December of that year, FDA Commissioner George Larrick informed the college that its NDA was denied because of misleading statements and omissions, because of inadequate manufacturing and control procedures, and because "safety has not been proven because of lack of proof of efficacy in diseases that are invariably fatal unless treated with adequate efficacious means" (112). While there was not a surfeit of bona fide treatments for the cancers Hepasyn claimed to benefit, there certainly were some. An approved yet ineffective Hepasyn, the reasoning went, would lead some patients to delay or possibly avoid treatment with established effective treatments. Larrick informed the mortuary school that if the NDA were not withdrawn, a hearing notice—as provided in the 1938 act to sponsors who wished to petition adverse NDA decisions by FDA—would be issued next month. Led by medical officer Barbara Moulton, FDA continued to assemble its case for a hearing. Medical director Albert Holland observed that this case "may well be a precedent-establishing case no matter which way the courts decide it." But in the end the courts would not have the opportunity, as the San Francisco school withdrew the application rather than face the hearing (113).

FDA had another chance to press the safety-efficacy policy a few years later, and this time the drug firm was more accommodating. On September 9, 1959, FDA approved Eaton Laboratories' application for Altafur (furaltadone), a systemic antibacterial agent. However, FDA's reevaluation of the NDA as a rising number of neurological and other adverse reactions came to light led the agency to question

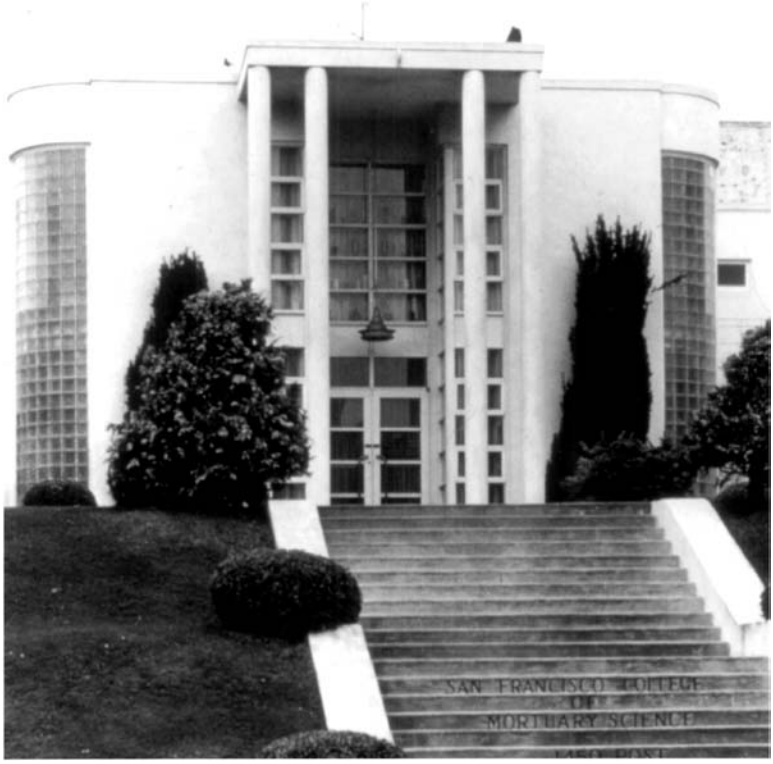

FIGURE 5 The San Francisco College of Mortuary Science served as the manufacturer, ambulatory clinic, and new drug application sponsor for a cancer treatment. FDA used this opportunity to press for a formalized policy mandating an efficacy requirement in some drugs. *Source*: Courtesy of the San Francisco History Center, San Francisco Public Library.

the efficacy of Altafur (114). Among other issues, FDA believed there were insufficient reports in the application from experts in the treatment of infectious diseases, and certain claims would have required unattainable plasma levels even at triple the recommended dosage. The agency did not explain why these issues were not apparent at the time of the application.

Eaton Laboratories submitted additional data, but FDA said that evaluation of those data should be done in the venue of a formal hearing over suspension of the Altafur NDA; its lack of effectiveness did not justify its toxicity. The hearing began in January 1961 and lasted several weeks. The hearing examiner was persuaded by the testimony of Maxwell Finland of Harvard, George Jackson of Illinois, and other experts on infectious diseases who disputed Altafur's claim of therapeutic value. The examiner decided that efficacy was indeed relevant to Altafur's safety considering the diseases treated—diseases amenable to effective treatment by other, less toxic drugs on the market. The NDA for Altafur was suspended in August 1962,

less than 2 months before Congress passed the Kefauver–Harris Drug Amendments (115,116).

KEFAUVER, KEVADON, AND A NEW APPROACH TO DRUG REGULATION

Estes Kefauver of Tennessee was not the first senator to voice concern about the increasing cost of drugs. Fellow Democrat Warren Magnuson of Washington had heard complaints from constituents and also learned about the rising cost of drugs in America as a member of the Labor, Health, Education, and Welfare Subcommittee. But Kefauver, chairman of the Subcommittee on Antitrust and Monopoly since January 1957, was in a position to explore this development in depth. Thus, in December 1959, following an extensive investigation by his staff that began the previous year, Kefauver initiated hearings into administered prices in the pharmaceutical industry. The early testimony provided some headline-grabbing statistics into how the pharmaceutical industry arrived at drug prices. For example, the committee learned that the German firm Schering had purchased bulk estradiol progynon (for symptoms associated with menopause) from Roussell of France for resale in the United States. When the committee compared the cost of the bulk product and what Schering charged for tablets produced therefrom, they discerned a markup of 7000% (117). The Schering president objected that such a hyperbolic figure ignored the costs of manufacturing, advertising, distribution, and research on this drug. Kefauver replied that Schering would have incurred no research costs for this Roussell drug itself.

When the hearings shifted into a study of drug costs as a function of research expenses in the industry, A. Dale Console, a former medical director at Squibb, testified that research indeed leads to many failures, but that "the problem arises out of the fact that (firms) market so many of their failures" (118). The hearings thus took on another dimension by investigating advertising practices of the pharmaceutical industry and the delivery of information about their drugs to doctors. Records subpoenaed by Kefauver from the 22 largest firms revealed that in 1958 they expended an average of one-fourth of their gross income on advertising. Investment in detail men represented a considerable portion of that expense, as estimates for the same year indicated a detail force for the industry of 15,000, or one for every 10 doctors (119).

The committee also heard about the relationship between FDA and the pharmaceutical industry. Former FDA medical officer Barbara Moulton described an acquiescent agency, frequently and inappropriately deferring to the wishes of firms. The committee's inquiry into Henry Welch, director of the Antibiotic Division at FDA who developed a lucrative business in medical reprint sales with drug companies, revealed a high-ranking regulatory official who was, at minimum, far too cozy with regulated interests (120). After 10 months of hearings, Kefauver's committee had raised a number of concerns, concerns that soon would be reflected in proposed legislation, introduced by Kefauver on April 12, 1961 (121–124).

Kefauver first addressed patents in his bill, severely curtailing the monopoly that drug companies would have on their products (an outgrowth of another facet of the hearings). The bill also gave FDA increased authority over drug production, distribution, and advertising. Food and Drug's inspection authority would be enhanced to uphold stronger quality-control standards in a system reminiscent of that applied to biologics. Advertising would include explicit and prominent warnings, again responding to problematical issues during the hearings. The law would

extend FDA's role for batch certification of selected antibiotics to all such drugs, not just those covered by the amendments up to the early 1950s. The drug clearance provision of the 1938 act, in which a drug application became effective after 60 days unless prevented by specific FDA action, would be ended under this bill. Finally, sponsors would have to show drugs to be effective as well as safe (125).

Opposition emerged quickly. The AMA, for example, came out strenuously opposed to the effectiveness requirement, arguing that only the physician can make a determination if a drug works or not. The industry, operating in part through its trade association, the Pharmaceutical Manufacturers Association, worked vehemently against elements of the bill that would affect its profits and force firms to advertise a drug's adverse reactions as well as its indications. The support of the White House was tepid at best (126). The process of negotiation, dilution, and revision ensued once Kefauver's bill cleared his subcommittee, proceeded to a parent committee, and then to the full Senate. However, unbeknownst to Kefauver and his colleagues, at this time a drug disaster was developing that would have an impact on Kefauver's law analogous to the legislative effect of the Elixir Sulfanilamide tragedy.

On September 12, 1960, the William S. Merrell Company of Cincinnati submitted an application for Kevadon, known generically as thalidomide. Merrell was the U.S. licensee for the German firm Chemie Grünenthal, which introduced this sedative in Europe in 1956. The application was routed to Frances Kelsey, who had replaced Barbara Moulton. Kelsey's superiors believed that this apparently straightforward NDA would be appropriate for a newcomer. However, Kelsey found the chronic toxicity data inadequate to support the safety of the drug and the labeling unsuitable. Merrell continued to append data to the application, which Kelsey continued to find inadequate to the task. The contacts between Merrell and Kelsey or her superiors thereafter occurred almost weekly until the spring, as the firm was rushing to make March 1 launch date for Kevadon. At this time, Kelsey also was deeply involved in FDA's administrative hearing with Eaton Laboratories over Altafur.

But crucial news emerged in February 1961, when the medical officer read a report in the December 1960 issue of the *British Medical Journal* that associated long-term use of thalidomide with peripheral neuritis. When representatives from Merrell met with Kelsey in May to discuss this revelation (which Merrell believed rather inconsequential, assuming the effects were reversible), Kelsey requested evidence that Kevadon would be safe in pregnancy. Although the request was based on a theoretical consideration stemming from the neurological side effect, it was consistent with Kelsey's own training as a pharmacologist at the University of Chicago, and it was shared by her medical officer colleagues at FDA. Merrell and outside clinical investigators representing the company continued to argue that Kevadon was effective and safe relative to the barbiturates, the firm now hoping to meet a November 1961 launch in time for the holidays.

On the last day of that month, Merrell reported to Kelsey that thalidomide had been withdrawn from Germany, where use of the drug had been correlated with severe congenital abnormalities. On March 8, 1962, Merrell withdrew its NDA for Kevadon. The United States narrowly escaped the fate of many other countries. But the agency learned in April for the first time the true scale of Merrell's investigation. Over 1100 doctors received Kevadon (the agency had assumed from three to six dozen investigators were involved), and the investigation involved about 20,000 patients, 624 of whom were pregnant. Despite assurances by Merrell that a recall

had been completed, field investigators discovered that over 25,000 doses were still unaccounted for in August, prompting an Elixir Sulfanilamide–like national search for outstanding samples of the drug. Seventeen cases of thalidomide-induced phocomelia occurred in the United States, seven of which were documented to be caused by thalidomide obtained outside the Merrell study (127–129).

The shock of what might have happened with thalidomide wrested the drug regulation reform bill from congressional inertia, and President Kennedy, surrounded by Kefauver, Kelsey, and others, signed the bill into law on October 10, 1962 (130) (Fig. 6). Although much had changed in the bill Kefauver introduced, still some elements remained. Attempts to cut costs via patent adjustments were long gone, as was the biologics-like system of licensing (although firms had to register). Manufacturers had to prove that their drugs were effective as well as safe—not just drugs introduced from that point forward, but all new drugs introduced since 1938. FDA's control over the clinical investigation of drugs was clarified and strengthened, and a surprise provision required experimental subjects to give informed consent. Safety, effectiveness, and reliability of a drug would be further provided for by requiring that production adhere to current good manufacturing practice, although that provision was made clear in FDA regulations as far back as the early 1940s (131). New drug clearance would no longer be based on an application becoming effective automatically after 60 days unless FDA action indicated otherwise; a new drug now could be marketed only with FDA's assent. Oversight of prescription drug advertising was transferred from FTC to FDA. And finally, drug inspectors

FIGURE 6 President Kennedy hands Senator Kefauver one of the pens used to sign the 1962 Drug Amendments. Among those looking on is Frances Kelsey, standing second from left.

would have enhanced access to establishment records other than financial or personnel documents (132).

CONCLUSION

The 1962 law was a landmark in the history of drug regulation, and no law since then has been as sweeping in its coverage of the pharmaceutical enterprise. But subsequent laws and regulations stand out, too, for many reasons. For example, the rise in the consumer movement certainly had an impact on drug regulation. The issuance of one of the first patient package inserts in 1970 for oral contraceptives followed pointed protest by women's health advocates against AMA's opposition to this precedent in patient education (133). The Vitamins and Minerals Amendment (Proxmire Amendment) of 1976, which prevented FDA from limiting potency of supplements or regulating them as drugs, was due in no small part by organized efforts of consumers to inundate their members of Congress and FDA with letters of protest on a scale unheard of at that time (134,135). The National Organization for Rare Disorders led the effort behind the Orphan Drug Act of 1983 to persuade pharmaceutical companies to develop drugs, otherwise unprofitable, for diseases with small patient populations (136,137).

In the same year, as part of an overall revision of investigational new drug (IND) procedures (the IND rewrite), FDA proposed so-called treatment-use INDs, expanding physician and patient access to experimental drugs for therapeutic rather than investigational purposes in patients "with serious diseases or conditions, for whom alternative therapies do not exist or cannot be used" (138–140). However, there were several restrictions to treatment INDs, such as the need to have a firm request treatment IND status, to be treated by a physician skilled in therapy of that disease, and to have no other therapies available. Activists representing HIV and AIDS victims, families, and friends engaged FDA directly on this issue and helped not only to relax these restrictions but also to refocus the overall drug development and evaluation process. FDA thereafter would consult with sponsors to plan more efficient clinical studies of drugs for life-threatening and severely debilitating diseases, modeled on the testing and evaluation of AZT (zidovudine approved in 1987 for patients with HIV) (141,142). Moreover, continuing pressure by AIDS activists for expedited access to experimental therapies figured in a policy announced by FDA Commissioner Frank Young in July 1988. Individuals would be allowed to return to the country with a 3-month supply of any drug desired as long as the agency ensured that the product was not fraudulent, counterfeit, or harmful, and if the traveler presented the name and address of the physician responsible for the treatment. The volleying over IND and NDA policies between FDA and the AIDS community continued into the 1990s (143).

The history of drug regulation has come full circle, from the second decade of the 19th century, when a Maryland physician persuaded Congress to pass a law to ensure genuine smallpox vaccine, to the first decade of the 21st century, when the United States again faced smallpox vaccination as a policy issue. In between we have witnessed a vast array of stimuli to changes in the way drugs are regulated. Therapeutic disaster and concomitant outrage, of course, are perhaps the most visible sources for tectonic shifts in policy. But political upheaval, organized social action, institutionalization of professional authority, the political and economic strength of the drug industry, the will and whims of all three branches of

government, the manner in which the fourth estate captures and conveys regulatory issues, and basic shifts in therapeutics itself all have had an impact on the way this country regulates drugs. FDA often refers to itself as a science-based regulatory agency, but the context for drug regulation over the past 200 years has been and will always be much broader than science and law.

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2 Modernizing the Food and Drug Administration

Arthur Y. Tsien, Esq.
Olsson Frank Weeda Terman Bode Matz PC, Washington, D.C., U.S.A.

INTRODUCTION AND OVERVIEW

In recent years, Congress has enacted and the president has signed into law a number of significant changes to the Federal Food, Drug, and Cosmetic Act (FDC Act) to modernize the Food and Drug Administration's (FDA) regulation of drugs and biological products. This chapter summarizes the significant changes.

These legislative changes began with the Prescription Drug User Fee Act of 2002 (PDUFA) (1), enacted in October 2002. PDUFA imposed user fees and other fees related to the review of new drug applications. In exchange for paying user fees, drug sponsors got the benefit of substantially shortened review times in the form of "performance goals." PDUFA has been enhanced and reauthorized three times since its inception, so that the current program is authorized until 2012. The major impact of PDUFA on FDA's drug review process is discussed in chapter 8.

The Food and Drug Administration Modernization Act (FDAMA) (2), enacted in November 1997, made substantial changes to FDA's practices and procedures. FDAMA was discussed in detail in chapter 6 of the first edition of this book.

The Best Pharmaceuticals for Children Act (BPCA) (3), enacted in January 2002, revised and reauthorized the 6-month pediatric exclusivity provisions added to the FDC Act by FDAMA. These changes are discussed in section "Pediatric Studies Exclusivity" of this chapter.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (commonly called the Bioterrorism Act) (4), enacted in June 2002, provided for the accelerated approval of drugs and biologicals to be used in the event of a bioterrorism attack or similar public health emergency. These provisions are discussed in section "Accelerated Approval of Priority Countermeasures" of this chapter. It also required public disclosure of a drug or biological sponsor's failure to fulfill its commitment to conduct postmarketing studies. These provisions are discussed in section "Reports of Postmarketing Approval Studies" of this chapter.

The Pediatric Research Equity Act (5), enacted in December 2003, gave FDA the statutory authority to require sponsors of applications for drugs and biologicals to conduct clinical studies to assess the safety and effectiveness of their products in children. These provisions are discussed in section "Mandatory Pediatric Assessment" of this chapter.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (6), enacted in December 2003, made fundamental changes to 180-day exclusivity for abbreviated new drug applications (ANDAs), including circumstances under which 180-day exclusivity is forfeited. The MMA also revised statutory provisions regarding the timing of the notice of a Paragraph IV certification given to the patent owner and the holder of new drug application (NDA) referenced