

The Impact of Novel Products on Federal Regulations
Controlling Drug Production: 1906-1963

by

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Introduction: What are Drugs?

Humans have sought to harness and use the therapeutic properties of botanical substances since ancient times. Eventually, people began trading and selling drugs to medical professionals and the public. By the beginning of the nineteenth century, numerous companies sold drug products on the American market, and drug products had become a sector of the commercial market. These drug products included botanical medicines, homeopathic remedies, and chemicals sold to cure ailments.¹

Meanwhile, scientists began establishing and refining techniques for analyzing chemical compounds and understanding the human body.² The isolation of morphine from opium by a German apothecary in 1805 illustrates the shift towards creating, rather than collecting, drugs. Funded by academic institutions and private laboratories, chemists discovered how to analyze the composition and structure of chemical compounds. Their discoveries allowed them to estimate the arrangement of individual atoms within newly isolated chemicals. Over the course of the nineteenth century, researchers refined this core principle of modern biochemistry, allowing scientists to link the chemical structure of compounds to their physiological function in the human body. This enabled medical researchers to create, discover, and produce thousands of drug products in the twentieth century. As chemists and physiologists discovered and synthesized new drug compounds, businesses packaged and sold these chemicals as drug products. In this thesis, I explore how several novel drug products

¹ Paul Starr, *The Social Transformation of American Medicine*, (Basic Books, 1982). 32, 48.

² John Parascandola, "Alkaloids to Arsenicals," in *The Inside Story of Medicines*, ed. Gregory Higby and Elaine Stroud, (Madison, WI: American Institute of the History of Pharmacy, 1997), 79.

influenced the federal government's regulation of the production of drug products between 1906 and 1963.

Over the course of the twentieth century, the term *drug product* came to represent an increasingly specific concept. Early in the century, any businessman or medical practitioner could design and sell a mixture of consumable materials as a disease cure without public dispute or legal repercussion. However, during the first half of the century, the public came to regard *drug products* as scientifically developed and clinically proven therapeutic agents used to treat diseases and ailments. The merit of drugs and drug products came to depend upon the extent to which they could be used to treat human diseases and ailments. For example, drug products containing penicillin gained unprecedented commercial success in the 1940s, because these products cured ailments like pneumonia, and not because of successful labeling or advertising. In prior decades, drug products often became popular for these reasons.

Drug products always varied in therapeutic merit. Faith in unconventional medicine and the potential for profit prompted the creation and sale of countless ineffective drug products throughout the nineteenth and twentieth centuries. However, during the twentieth century companies produced increasingly effective drug products, as shown by the increased average life span in America. Effective antibiotics, including penicillin, reduced the mortality of common infectious diseases

like meningitis, tuberculosis, and pneumonia. Between 1900 and 1960, the average life span of American increased by over twenty years, from 49.2 years to 69.9 years.³

This thesis argues that the commercial success of specific drug products during the first six decades of the twentieth century determined the content of federal drug regulations in the United States. In the in the 1900s, 1930s, and later decades, the commercial success of specific products made legislators aware of certain products and demonstrated to them how the law impacted (or did not impact) the production of drug products and how this relationship could influence the public health. The commercial success of products also changed the public perception of what drug products could be and could do therapeutically. Changes in scientific research and technologies, changes in societal expectations, and other cultural shifts prompted the creation and sale of new drug products during the twentieth century. Certain novel drug products, namely sulfanilamide, penicillin, and Krebiozen, altered the public's conception of *drug products* enough to prompt legislative change. In saying that products prompted legislative change, I argue that they both determined the content of these regulation and caused their passage in Congress. Although people have understood drugs as therapeutic agents used to treat diseases throughout history, legislators did not link drugs with science until the twentieth century.

*

I construct this thesis around the notion that *drug production* is a multistep process that creates drug products. A drug, or drug compound, is a substance that

³ Elizabeth Arias, "United States Life Tables, 2006," *National Vital Statistics Reports* 58 no. 21 (Hyattsville, MD: National Center for Health Statistics, 2010), 25-28. In contrast, the average life span of Americans increased by less than eight years between 1960 and 2006.

induces a physical effect on the human body; a drug product is an article sold to the public as a therapeutic that contains one or more drug compounds and usually other inactive compounds. This process involves scientific researchers, drug manufacturers, pharmacists, physicians, and patients. The development, manufacture, sale, and use of drug products comprise the process of *drug production*. Drug development entails the discovery or creation of drug compounds, *in vivo* assays of the drug's therapeutic value, *in vitro* studies of the drug's therapeutic value, animal testing, and clinical trials using human subjects. Drug manufacture entails the actual construction of drug products, including the blending of drug compounds with inactive compounds to create a liquid or pill for consumption. Drug manufacture determines the strength, purity, and quality of the drug compounds in drug products. The sale of drug products encompasses the labeling of drug products for sale to the public or pharmacists, and the advertising of drug products. The use of drug products may involve simply the patient's purchase and consumption of the product. Drug use may also entail a more complicated process of a physician's prescription and a pharmacist's distribution before the patient purchases and consumes the drug product.

This thesis describes how the federal government came to regulate many aspects of the development, manufacture, sale, and use of drug products in America between 1906 and 1963. The traditional historical narrative of American drug regulation recounts the establishment of three major pieces of legislation in the twentieth century: the 1906 Pure Food and Drug Act, the 1938 Food, Drug and

Cosmetic Act, and the 1962 Drug Amendments.⁴ These statutes established the structure of the system of drug development and production used today. I argue that the commercial and scientific reception of specific drug products determined the content of these regulations, along with several other amendments to these laws. This thesis offers a narrative of the development of drug regulation in twentieth century America informed by changes in medical science and the content of the drug market. The commercial success of and the perceived dangers to the public health owing to specific drug products dictated the manner in which the government conceived, passed, and enforced drug regulations.

Chapter One focuses on the establishment of the first federal drug laws enacted between 1906 and 1938. It begins by discussing the private organizations that monitored the drug market before the enactment of the first federal drug law in 1906. I argue that these private organizations shaped the manner in which legislators crafted the 1906 Pure Food and Drugs Act. Legislators first reacted to the growing drug market of the 1900s by regulating the labeling of drug products. In the 1930s, they passed new legislation responding to the advent of sulfonamide drugs and to the idea that drugs ought to be scientifically developed. In 1938 the federal government began regulating drug products as scientific products by controlling the ways in which firms could develop drug products.

Chapter Two focuses on how the development of major effective drug compounds impacted the regulation of drug products in the 1940s. During this time

⁴ Peter Temin, *Taking Your Medicine*, (Cambridge: Harvard University Press, 1980); Stephen Ceccoli, *Pill Politics*, (Boulder, CO: Lynne Rienner Publishers, Inc, 2004); Harry Marks, *The Progress of Experiment*, (New York: Cambridge University Press, 1997).

infectious disease was the greatest threat to American lives. Medical researchers worked to discover drug compounds that could treat infectious diseases effectively, especially during the Second World War. During this decade the government established federal programs to certify batches of drug products containing insulin, penicillin, and other antibiotics. In 1951 the federal government enacted the first law mandating that pharmacists distribute certain (nonnarcotic) drugs only with a written physician's prescription. I argue that the medical and commercial success of drug products containing penicillin and streptomycin, the first antibiotic drugs, prompted legislators to increase the scope of federal drug regulations to include the manufacture and sale of drug products. Penicillin and streptomycin caused legislators to become concerned with the consistency of these products and to recognize that further regulating these products could benefit the public health.

Chapter Three argues that two very different drug products, Kevadon (thalidomide) and Krebiozen, prompted legislators to regulate the development of drug products. Medical researchers' use of these drugs in clinical trials convinced legislators that the investigation of a drug's safety and therapeutic merit on human subjects warranted federal regulation. Krebiozen and Kevadon demonstrated to legislators that investigators could distribute any drug product to patients if they were involved in clinical trials on that product, despite documented concerns about the product's safety or efficacy. By 1963, the federal government controlled how pharmaceutical firms developed, manufactured, and labeled drug products.

I argue that the expansive distribution and commercial success of specific products on the drug market shaped the content of American drug regulations in the

twentieth century. This is not to say that the regulations themselves have not affected the quantity, quality, or types of products available on the market. The regulations I consider changed the nature of the bulk of drug products available on the market drastically. However, the discovery of several specific, unprecedented drug compounds and the production of drug products using these compounds determined the subject and goals of the major drug regulatory laws passed between 1906 and 1963.

While I focus principally on the regulations enacted in 1906, 1938, and 1962, I also discuss the effects of a series of lesser regulations. These include the 1914 Harrison Narcotics Act, the 1941 Insulin Act, the 1945 Penicillin Act, the 1951 Durham-Humphrey Amendment, and the 1963 Investigational Drug Regulations. This thesis focuses on the first sixty years of federal drug regulations because during these years the government established the modern drug regulatory system. This system uses a premarket approval system in an attempt to ensure the safety and effectiveness of all drug products, which most people take for granted today.

Although this system has been amended considerably over the past fifty years, the Food, Drug and Cosmetic Act remains the foundation upon which new regulatory programs are built. By illustrating how specific drug products and trends in drug products have prompted and determined federal regulations, I argue that the modern American drug approval and regulation system was not inevitable. Legislators created this system by reacting to specific drug products, rather than by considering the future of the drug market. This thesis concludes that Congress would not have created the

federal drug regulatory system in place today without the existence of the sulfonamides, penicillin, streptomycin, Kevadon, and Krebiozen.

Chapter One: Regulating the Sale of Drug Products: 1900-1938

Introduction

In 1906 the Pure Food and Drugs Act became the first federal law to regulate the sale of medical drugs in America. Independent professional organizations, however, had begun monitoring the drug market almost a century before the enactment of this statute. These professional organizations lacked legal authority, yet they managed to influence both the production and use of drugs in America. The earliest monitoring of the production of therapeutics in America came from the editors of the *United States Pharmacopeia (USP)*, who published a list of therapeutics accepted by an organized group of physicians, pharmacists, chemists and physiologists. Beginning in 1820, the *USP* editors used a set of standards to assemble a list of drugs they believed had therapeutic merit specifically for the use of physicians. The inception of the *USP* represents the first private action taken towards systematically inspecting the safety and effectiveness of drug products available to physicians in America.

This chapter demonstrates how public drug regulations developed out of private drug regulatory schemes. Although states regulated the sale of drug products in the nineteenth century, Congress did not enact federal drug regulations until 1906.⁵ This chapter focuses on the drug products sold during the first forty years of the twentieth century and the federal statutes that the distribution, widespread use, and

⁵ The development and enactment of state laws regulating drug products are beyond the scope of this thesis.

commercial success of these products prompted: the 1906 Pure Food and Drugs Act and the 1938 Federal Food, Drug and Cosmetic Act (FDCA). In the early 1900s, physicians and the public had access to a large quantity of drug products that varied in packaging, safety, and effectiveness. The public supported government attempts to regulate drug products because they believed the state could ensure their safety. However, Congress focused on enacting legislation to standardize the labeling practices of drug manufacturers. This preoccupation with labeling prevented Congressmen from enacting legislation regulations that prevented the sale of dangerous drug products in 1906.

Despite the flaws of the 1906 Act, Congress did not attempt to pass major new federal drug regulations until the 1930s. I argue that Congress did not attempt to amend the regulations until this point because the products on the American drug market did not change substantially in the 1910s and 1920s. Congressmen and reformers did not have a new type of drug product on which to base legislative change until the 1930s. While medical researchers developed new products in the 1910s and 1920s, the public did not begin using these products regularly until the following decade. These new products included anti-infective agents, the most notable of which were the sulfonamides, or sulfa drugs. Physicians used drug products containing the sulfonamides to treat infectious diseases like syphilis and respiratory infections. The commercial and medical success of the sulfa drugs prompted legislators to implement regulations that defined drug products accepted by the government more thoroughly. The medical success of these products caused physicians to support their use and to call for regulations removing ineffective

products from the market. The increasing authority of the medical profession throughout the course of the twentieth century allowed for them to influence the content and enactment of drug regulations to a greater extent in the 1930s than in the 1900s. The commercial success of these products made legislators aware of their existence, and the potential for effective drug products, which allowed them to consider the safety and efficacy of drug products in regulating their production. Moreover, the development of sulfa drugs prompted a shift in the public understanding of drug products from mere commercial entities to scientifically developed commercial entities. In passing the FDCA in 1938, legislators began regulating drug products with legislation that addressed how companies how used science to produce drug products. Specially, the FDCA initiated the regulation of the development of drug products; however, this power remained limited until the 1960s.

Private Drug Industry Regulations before Public Regulation: The *USP* and the AMA

Using the USP to Differentiate Patent Medicines and Ethical Drugs

The editors of the *USP* monitored drug products before any other organization in America. Although this publication had little impact on drug manufacturers, it began the process of differentiating between the therapeutics accepted and rejected by the scientific medical community. The content of the early *USP* provides a textual basis for historians to differentiate between two types of drug products: ethical drugs and proprietary medicines. During the nineteenth century the *USP* contained entries

for a range of botanical and chemical compounds. Chemists isolated some of these compounds from botanical items and synthesized others within the laboratory. Medical professionals defined ethical drug products as those containing only drug compounds that had been shown to have some effect on the human body, such as morphine or aspirin. The *USP* provided standards of purity and strength to guide physicians and companies in preparing ethical drug products from these compounds. In the nineteenth century, ethical drug products usually contained a single drug compound sold as a liquid or pill. The *USP* functioned to specify the ingredients that companies could use to create ethical drug products. The *USP* did not contain entries for drug products. The most prevalent drug products on the market in the nineteenth century were proprietary or patent medicines. The terms “patent medicine” and “proprietary medicine” both refer to a category of products sold in America as medical therapeutics into the first half of the twentieth century.⁶ The public used the term “patent medicine” because of the manufacturers’ secretiveness concerning the content of their products. They used the term “proprietary medicine” because of the tendency of manufacturers to use people’s names in titling their products, using names such as Hood’s Sarsaparilla or Carrington’s Life Pills. Although popular understanding today decries proprietary medicines as worthless and dangerous, both ethical drugs and proprietary medicines of the nineteenth century were inconsistent in their safety and effectiveness. Ethical drugs and proprietary medicines differed most in the manner in which their makers marketed and labeled them.

⁶ I will use the terms patent medicine and proprietary medicine interchangeably.

Though historians have characterized the patent medicine industry as unscientific and purely profit rendering, its products varied greatly. One cannot generalize about patent medicine makers beyond their use of direct to consumer sale.⁷ Manufacturers sold patent and proprietary medicines directly to the consumer; they could be purchased at corner stores, grocers, and pharmacies. Manufacturers of ethical drugs sold their products to pharmacists to dispense to the public through physicians' prescriptions.⁸ Proprietary medicines contained mixtures of various substances, unknown to the consumer or physician. Manufacturers labeled these products with often-unsubstantiated medical claims. They maintained that their products could treat or cure a variety of diseases including blood sickness, cancer, tuberculosis, sleeping sickness, scurvy, malaria, cholera, consumption, scrofula, and pneumonia. Proprietary medicine makers also marketed their products as a means to improve one's quality of life, rather than cure a specific ailment, using terms like "soothing syrup," "sleep aid," and "masculinity builder". The roots of patent medicine manufacturing can be traced back to colonial times, but their success ballooned in the early nineteenth century.⁹

By the 1900s, the *USP* included entries for a range of isolated chemical compounds (digitalis, phenyl salicylate, copper sulfate, magnesium oxide), and single

⁷ Courtney Fullilove, *The Making and Unmaking of the US Pharmacopeia*, CHUM Lecture Series: Fact and Artifact, Wesleyan University, Middletown, CT, November 28, 2011.

⁸ A. Walker Bingham, *The Snake-Oil Syndrome: Patent Medicine Advertising* (Hanover, MA: The Christopher Publishing House, 1994), 3-6.

⁹ James Harvey Young, *The Toadstool Millionaires* (Princeton: Princeton University Press, 1961), 3.

elements (iron, barium, potassium) found to have some effect on the body.¹⁰ The *USP* editors listed the amount and purity of these drug compounds they believed physicians should use in treating patients. These drugs acted principally as treatments for ailments, often by inducing vomiting, sweating, and bowel movements, or by increasing hunger. These physiological effects could indirectly aid in coping with or ridding the body of an ailment, even if they did not have a direct effect on the disease-causing pathogen. Opium reduced pain, magnesium oxide was a laxative, and aspirin reduced both pain and swelling.

In publishing the *USP*, its editors asserted that the scientific medical community believed that physicians should use only the drug compounds listed to treat patients' ailments. They implicitly denounced patent medicines containing a range of unknown ingredients, even though patent medicines often contained some of the drug compounds listed in the *USP*. Ethical drugs, also known as "official drugs" because of their inclusion in the *USP*, were often not perfect or even effective, but were created through the use of contemporary research in chemistry, biology, and physiology. Patent medicines often contained dangerous additives like alcohol, chloroform, hashish, and opium. Taking either patent medicines or ethical drugs could cause serious health issues for patients, including dependence and illness. In 1888 the American Pharmaceutical Association (APhA) began publishing the *National Formulary (NF)*, a list of drug products available on the American market.¹¹ The *NF* included botanical compounds, drug compounds, ethical drugs, and proprietary

¹⁰ Convention of the United State Pharmacopeia, *United States Pharmacopeia*, (Philadelphia: Lippincott, Grambo & Co, 1851).

¹¹ American Pharmaceutical Industry, *National Formulary*, (American Pharmaceutical Industry, 1888), iii.

medicines. The APhA published the *NF* to provide pharmacists with a list of all available drug products.

Endorsing the Ethical Drug Industry as a Scientific Enterprise: The AMA in the 1900s

The American Medical Association (AMA) became the next professional organization after the *USP* publishing committee to monitor the drug industry. In the second half of the nineteenth century the AMA emerged as body of young physicians attempting to regulate entrance to the medical profession. Early AMA leaders championed the use of ethical drugs and the scientific principles that supported their use, including germ theory. During the second half of the nineteenth century, Americans who identified as “physicians” ranged widely in their level of education, skills, and outlook on treating patients. No organization had yet emerged to define or standardize the profession. Paul Starr has recounted the successful campaign by AMA leaders to consolidate and standardize the medical profession.¹² Examining this crusade for professional sovereignty, while not directly related to the contemporaneous rise of drug regulations, provides insight into the relationship between physicians and drug products at this time.

Established in 1847, the AMA aimed to unify physicians nationally. The organization spent most of its first hundred years attempting to establish greater professional authority for physicians. I take the views of AMA leaders and members as representative of physicians because they reflect the views of practitioners who

¹² Starr, *The Social Transformation*.

mostly closely resemble modern physicians. AMA leaders advocated for monitoring and evaluating drugs products.¹³ These leaders recognized the need to analyze drug products as a means to better educate physicians. As detailed in the previous section, drug products varied immensely in their effectiveness, safety, and origin in the nineteenth and early twentieth centuries. AMA leaders and other reformers held ethical drug manufacturers in high regard and criticized the patent medicine industry harshly. AMA leaders supported the use of ethical drugs because the developers of these products used the same scientific principles in developing drug products that the AMA believed should be taught to physicians.

In 1907 the editor of the *Journal of the American Medical Association* (*JAMA*), George H. Simmons, wrote of the drug products available on the market:

A few of these, we may admit, have a distinct value... The vast majority, however, are but the simplest of mixtures or are well-known drugs put out under fanciful names, with no advantage whatever; or are absolute frauds and swindles... [made by men] who know nothing about medicine, pharmacy or chemistry, and who have gone into the business as they might have gone into any other get-rich-quick enterprise... But worse than the increase in number is the development in the advertising literature of unblushing falsehood and palpable deception.¹⁴

Simmons' views are representative of the views of AMA leaders in the 1900s. They scorned the patent medicine industry for their lack of use of scientific principles in developing drug products and their desire for profit. Just as AMA leaders feared their own displacement due to the popularity of untrained doctors and homeopaths, they also feared the displacement of ethical drugs by proprietary medicines. The AMA

¹³ Morris Fishbein, ed., *The History of the American Medical Association*, (Philadelphia: W.B. Saunders and Company, 1947), 214-259.

¹⁴ George H. Simmons, "The Commercial Domination of Therapeutics and the Movement for Reform," *Journal of the American Medical Association* 48, no. 20, (1907): 1645.

avoided any connection with the seemingly unscientific, profit-rendering proprietary medicine industry. AMA leaders continued to promote the products of the ethical drug industry by introducing their own system of inspecting drug products.

Monitoring the Effectiveness of Drug Products: The AMA in 1905

The AMA created the Council on Pharmacy and Chemistry (CPC) in 1905 to investigate drug products and assess their therapeutic effects. In 1907, George Simmons described the CPC as a group whose “energies are devoted to the thankless task of winnowing from the chaff of dishonesty the occasional grain of honesty.”¹⁵ The AMA created the CPC to increase the availability of information about drug products on the market for physicians. The Council produced a list of the drug products they believed were therapeutically effective in an annually published compendium called *New and Nonofficial Remedies (NOR)*. The CPC consisted of a board of sixteen professionals, including chemists, physicians, bacteriologists, pharmacologists, the editor of *JAMA*, and at least one representative from the United States Department of Agriculture (USDA). This shows that the federal government supported and cooperated with the CPC. Unlike the editors of the *USP*, the Council evaluated only those drugs whose manufacturers chose to submit them for inclusion in *NOR*. The submission included details about the product, studies done on its therapeutic value, and an actual sample of the drug for chemical analysis.

The publication of the *NOR*, the *USP*, and the *NF* demonstrate how independent professional organizations took actions towards regulating the drug industry before the enactment of federal regulations. *NOR* functioned as a physician’s

¹⁵ Simmons “The Commercial Domination,” 1646.

drug manual that judged the therapeutic value of products on the market. In contrast, the *USP* and the *NF* had functioned solely as sources on the composition of drugs for pharmacists, physicians, homeopaths, and the public.

Even though AMA leaders opposed the use of patent medicines, the CPC accepted submissions for any product. This displays the confidence of AMA leaders in their scientific methods of assessment; AMA leaders did not believe they could not completely eradicate patent medicines, and decided to focus their efforts on informing the medical profession about these products.¹⁶ The CPC included an inventory in *NNR* that listed ready-mixed drugs containing the ethical drugs of which they approved. Proprietary medicine makers often chose not to submit applications for their products because submission required disclosure of a product's ingredients. Many proprietary medicine firms did not want to reveal this information for fear of imitators. In this manner, the firms who submitted their products to *NNR* were self-selecting. Ethical drug preparations sourced from specific firms made up the majority of listed content of *NNR*.

The CPC used a published set of rules in evaluating drug products. The CPC's rules illustrate that while they were concerned with the safety and efficacy of drug products, they were equally concerned about how drug firms labeled and advertised their products. In applying for CPC approval, drug manufacturers provided the Council with a sample of the product and reports on their own assessments of the product's therapeutic merit. The CPC then performed scientific assays on the product

¹⁶ The products included in *NNR* were very similar to those included in the *USP* and consisted mostly of ethical drugs. However there was a gray area in between ethical and patent medicines and CPC program was more liberal about including drugs that skirted the line between ethical and patent medicines.

to determine if its therapeutic merit warranted acceptance. In the first years of the CPC's existence its investigators used the Hygienic Laboratory of the USDA's Bureau of Chemistry to perform chemical analyses on submitted drug products. These experiments aimed to determine the chemical identity of submitted products and assess their safety for humans. The Council also reviewed all information provided by physicians who had used the product to assess the product's therapeutic value. The Council mandated that the drug product labels contain all active medical ingredients and their amounts. Additionally the Council banned advertising directly to the public, all exaggerated or misleading statements, and false statements about sources, dangers, and therapeutic effects of drug products.¹⁷ The Council also rejected any products with labels that included the disease, or diseases, that the product intended to treat. This rule aimed to prevent the public from using drugs without a physician's recommendation.

Numerous medical journals, including *JAMA*, the largest medical journal in America and the second largest medical journal in the world, accepted advertisements only for drug products accepted by the CPC.¹⁸ Eventually, the CPC designed an "AMA Seal of Approval" emblem, which firms could use in labeling all products included in *NNR*. The AMA believed that *NNR* should be as complete as possible, so they were relatively liberal about accepting drugs.¹⁹ In establishing the Seal of Approval program and *NNR*, the AMA aimed primarily to change physicians'

¹⁷ *New and Nonofficial Remedies*, (1915): 8-11.

¹⁸ The largest medical journal at the turn of the twentieth century was the *British Medical Journal* published by the British Medical Association. Today *JAMA* has eclipsed the BMJ and has the largest weekly circulation of any medical journal in the world.

¹⁹ Simmons, "The Commercial Domination," 1646.

prescribing practices, not to change the nature of either the ethical or the patent medicine industries. The Council firmly stated in each *NNR* edition, “acceptance [of a product] is not an endorsement.”²⁰

The AMA works to uphold the best interests of physicians. An optimist could claim this is because its leaders believe physicians are the most important actors providing health care in America. One could also assert that the AMA works to uphold physician authority to maintain personal profits and power. Regardless of its motives, the AMA impacted the evolution of drug regulation in America in the early part of the twentieth century by establishing a precedent for using scientific analyses to determine the content, safety and effectiveness of drug products. Drug products will always affect the responsibilities of physicians, so it is in the best interest of the AMA to pressure the industry to conform to their own ideals about medicine. Eventually, in 1938, the federal government required that companies submit a similar application for all new drug products before they could sell them legally. Moreover, the CPC’s Seal of Approval Program provided a precedent that legislators could use to regulate firms use of science in developing drug products.

The CPC influenced the manner in which some pharmaceutical firms developed and marketed drug products. The CPC encouraged manufacturers to use scientific testing in developing their products. Although it would be over thirty years before federal mandates legally linked scientific analysis with drug production, the work of the Council began the process of encouraging firms to use scientific techniques to develop drug products. In practice, the CPC worked to discourage drug

²⁰ *New and Nonofficial Remedies*, (Chicago: American Medical Association, 1915): 3.

makers from advertising their products to the public, as proprietary medicine makers often did. The AMA's aversion to proprietary medicines stemmed not so much from the existence of these products, as from their opinion that their makers used excessive and deceptive advertising in selling these products. Federal legislators and reformers also worried about the potential deceitfulness of proprietary medicine companies.

Contemporary and past journalists and scholars have criticized the legitimacy of the AMA's Seal of Approval and the potential monetary motives of its founders, the *JAMA* editors George Simmons and Morris Fishbein. Without delving into the possible corruption of the work of the CPC and the Seal of Approval Program, I claim that the motives of AMA are of little consequence to the impact that the CPC had on modern drug regulations. My argument focuses on the AMA's monitoring of drug products and its impact federal drug regulations. The rules the CPC used to justify acceptance or denial of drugs into *NNR* illustrate that the physicians valued the use of scientific knowledge, experiments, and practices in developing drugs. Even if the AMA did not follow these rules precisely, the AMA still played a role in determining the popularity of drugs and the growth of the ethical drug industry. The work of the CPC influenced the content of the drug market in the first decades of the twentieth century by propagating the superiority of ethical drug products.

The battle between pharmacists and physicians over the authority to prescribe drugs compelled the APhA to begin publishing the *NF* and the AMA to create the CPC. Physicians, especially those in the AMA, used *NNR* to educate themselves about the drug products available on the market and to gain authority over

pharmacists in this field.²¹ The APhA published the *NF* for pharmacists as a resource on all drug products available, including ethical drugs and patent medicines. In publishing *NNR*, AMA leaders intended to provide an alternative, physician-oriented pharmacopoeia to *NF* and *USP*. The ethical drug industry supported the work of the AMA, as they wanted to increase the validity of their own products to differentiate themselves from the makers of unofficial and untested drugs.²² The ethical drug industry and AMA leaders increasingly used claims of rational development and clinically proven effectiveness to distinguish between ethical drugs and patent medicines.

Although the CPC was not a government regulatory agency, it regulated drug-prescribing practices from within the medical profession itself. The government supported the CPC's methods for evaluating drugs even after the enactment of the Pure Food and Drugs Act in 1906. In creating the CPC, the AMA emphasized the demands of the physician when creating a drug regulatory system, a precedent set by the *USP* editors. The AMA created the CPC only a year before the passage of the 1906 Act.

While the Council's actions provided a precedent for the pre-market approval system established by the government in 1938, the CPC did not significantly impact the 1906 Act. Legislators considered the interests of the consumer over the interests of the physician and the AMA in writing the Act; they regulated drugs as commercial

²¹ John Swann, "FDA and the Practice of Pharmacy: Prescription Drug Regulation before the Durham-Humphrey Amendment of 1950," *Pharmacy in History* 32 no. 2 (1994): 56-59; Starr, *The Social Transformation*.

²² Austin Smith, "The AMA Council on Pharmacy and Chemistry," in *The History of the AMA*, ed. by Morris Fishbein.

products and sought to provide the consumer with information on these products. The widespread use of both ethical drugs and patent medicines ultimately compelled legislators to regulate the commercial activities of this growing industry. The content of the drug market at the turn of the twentieth century prompted the creation of both the CPC and the enactment of the Pure Food and Drugs Act. The Act functioned to increase consumer awareness of the contents of drug products while the CPC functioned to educate and increase the authority of physicians.

Establishing the Federal Regulation of Drug Products

Public Monitoring of the Drug Industry: Harvey Wiley and the Bureau of Chemistry

In 1862 the USDA established the Bureau of Chemistry (BOC) to investigate a range of commercial products. The BOC was one of the first scientifically focused divisions of the American government and its creation demonstrates the government's increasing trust in using science to monitor the commercial market. The Bureau existed to determine the chemical and biological content of products using scientific analyses. Harvey Wiley served as the Chief Chemist of the Bureau from 1883 until 1912. He emphasized the use of scientific principles in government.²³ Moreover, Wiley advocated for the enactment of laws to regulate the food and drug industry. Under Wiley's guidance, the Bureau performed chemical experiments and trials on humans that demonstrated the danger of food additives and patent medicines. Despite this, Congress did not pass regulations prohibiting the sale of dangerous products until 1938.

²³ *FDA: A History*, DVD, directed by Greg Meyer, (Compliance Media, 2008).

In 1902, Congress enacted the first major law enforced by the BOC: the Biologics Control Act. This law authorized the Hygienic Laboratory of the Public Health and Marine Hospital Service to implement scientifically testable standards of safety, purity, and potency for the production of vaccines and antitoxins.²⁴ By 1903, chemists could perform assays to detect food and drugs additives known to be harmful, including arsenic- and lead-based pesticides, and numerous coal tar dyes. The Bureau used these techniques to monitor the industries, but it had no legal means to act on this information. Wiley and his staff could only inform consumers about the dangers of these products. During the late nineteenth century, Wiley published reports on the studies of the Bureau of Chemistry. These publications served to inform professionals and laypeople about the content of food and drug products on the market.²⁵ Despite the Bureau's efforts, consumers continued to purchase dangerous foods and drugs during the 1900s.

From the 1880s through the 1900s, Wiley and other Progressive-era reformers tried to enact legislation to regulate the drug industry. Although Wiley was most passionate about for the need for regulation of food additives, he advocated for a comprehensive bill regulating both the food and drug industries. Progressive reformers pushed for the passage of regulations governing the food and drug

²⁴ "Special Collaborative Issue," *CBER Vision*, Center for Biologics Evaluation and Research, July 1, 2002, accessed December 14, 2011, https://docs.google.com/a/wesleyan.edu/viewer?a=v&q=cache:2-uC6RYAt2cJ:www.fda.gov/downloads/aboutfda/whatwedo/history/productregulation/100yearsofbiologicsregulation/ucm070104.pdf+&hl=en&gl=us&pid=bl&srcid=ADGEESgzj5LLsOLUCT4Q6r4TY6UEOT3j6r0xZHGFo10koE3zywapD5Rd3tCK73o8HrJ8Dyp6B_NEv45Kw5uHMyFs-rRqwp-Q5LYD4DREGrDvXHq4e76BqNy9iYXcDngMD9Fe5NQ7ntlh&sig=AHIEtbQriyhK5UwXirssOD_qB35VZiIRgA&pli=1.

²⁵ *FDA: A History*, DVD.

industries as one of many public health reforms of the early twentieth century.²⁶ With respect to drug regulations, reformers emphasized the dangers of proprietary medicines and the need to control their sale. They wanted Congress to enact regulations that would protect the public health by limiting the sale of dangerous products and continuing programs to evaluate the safety of these products. The passage and enforcement of federal drug regulations corresponded to greater political movements of the time. The campaign for federal drug regulations arose from the Progressive Era ideal of a clean and controlled society. Although the dangers of patent medicines had become increasingly evident and publicized in the early 1900s, physicians and laypeople rarely considered the dangers of ethical drugs. However, all drug products posed a risk to patients.

By 1902, the appeals of Wiley and other Progressive reformers to the government to pass food and drug regulations had generated concrete Congressional discussion. Public health officials, food packers, agricultural organizations, the AMA, pharmacists, and the ethical drug industry supported industry regulation. Distilleries, food manufacturers, and the Proprietary Association of America, a group of patent and proprietary medicine manufacturers, however, all opposed the enactment of public drug regulations.²⁷ Reformers and physicians favored stronger regulation of industry, while most manufacturers did not want the federal government to regulate their commercial activities. Ethical drug firms supported regulation of the drug

²⁶ Michael McGerr, *A Fierce Discontent: The Rise and Fall of the Progressive Movement in America: 1870 – 1920* (New York: Free Press, 2003), 77-117.

²⁷ Wallace F. Janssen, “The Story of the Laws Behind the Labels,” *FDA Consumer*, June 1981; James Harvey Young, *The Toadstool Millionaires*, 107-108.

industry because they believed that increased restrictions on drug products would favor their products over patent medicines.

Ultimately, increased public awareness and governmental support propelled the passage of a law regulating the food and drug industries.²⁸ Reformers, AMA leaders, and members of the Bureau of Chemistry strived to increase public awareness of the hazards of food and drug products in the early twentieth century. Federal legislation aimed to increase the transparency of drug labeling and packaging to standardize the drug industry in the interest of the patient-consumer.

Passing the Pure Food and Drugs Act of 1906: Legislative History

Harvey Wiley played a central role in advocating for a food and drug law. However, he needed political support and sponsorship in order to get Congress to enact these regulations. Wiley successfully convinced members of Congress of the importance of a food and drug law. Between 1879 and 1906, legislators introduced almost one hundred bills into Congress intending to regulate the food and drug industries.²⁹ Colonel William Hepburn, a Republican representative from Iowa, introduced four bills during this time, including one that ultimately became the Pure Food and Drugs Act.³⁰ During the first session of the 57th Congress in 1902, Hepburn

²⁸ Both the 1906 Pure Food and Drugs Act and the 1939 Food, Drug and Cosmetic Act regulation more than just drugs. I will not speak directly about the changes in food manufacturing regulations; however, it is important to note that interest in the public health and the consumer's right to knowledge prompted regulation of foods and drugs, as well as cosmetics and medical devices in later years.

²⁹ John Swann, "The 1906 Food and Drugs Act and Its Enforcement," *FDA History*, Food and Drug Administration, accessed 15 December 2011, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm>.

³⁰ John Ely Briggs, *William Peters Hepburn* (The State Historical Society of Iowa: Iowa City, Iowa, 1919), 276-285). I sourced much of the legislative history of the 1906 Pure Food and Drugs Act from this biography of Representative Hepburn.

introduced “A Bill for Preventing the Adulteration, Misbranding, and Imitation of Foods, Beverages, Candies, Drugs, and Condiments,” (H.R. 3109), which intended to compel firms to market products truthfully and to inform consumers about the content of these products.³¹ The bill aimed to standardize the labeling practices of the food and drug industries by preventing the misbranding and adulteration their products. Hepburn attributed the text of the bill to a committee appointed by the National Pure Food and Drug Congress.³² Notably, an external, nonpermanent committee appointed by the Senate Committee on Interstate and Foreign Commerce also authored the 1933 bill that would eventually become the Federal Food, Drug and Cosmetic Act of 1938.³³

The debate over the regulation of drug labeling caused substantial debate and prevented Congressmen from considering introducing bills to regulate other aspects of the drug production process. Representative William C. Adamson of Georgia led opposition to the bill, claiming that it was overly paternalistic and unnecessary. Hepburn’s bill charged the USDA’s Bureau of Chemistry with its enforcement. Member of both the House and the Senate opposed this delegation of power. Other Congressmen believed the bill, if enacted, would allow the government to prosecute the owners of small markets when they accidentally sold mislabeled or adulterated products. The manufacturers of proprietary medicines opposed the passage of the bill because they believed it would hinder their ability to create and sell products. Lobbying by these firms convinced a number of Congressmen to challenge the bill.

³¹ Briggs, *William Peters Hepburn*, 277.

³² Briggs, *William Peters Hepburn*, 278.

³³ David Cavers, “The Food, Drug and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions,” *Law and Contemporary Problems* 6 (1939): 2-42.

Representative Champ Clark of Missouri, among others, supported the fundamental objectives of the bill, but argued Hepburn's bill was too drastic.

The large number of bills proposed by legislators in the first years of the twentieth century to regulate food and drug products impeded the passage of a single piece of legislation. In 1902, Senator Porter McCumber of North Dakota introduced a bill similar to Hepburn's bill numbered S. 88. McCumber and Hepburn focused their bills on standardizing labeling practices within the drug industry. The McCumber bill competed with Hepburn's bill in the Senate and played a role in preventing the passage of H. R. 3109; however, both bills received strong opposition. The House passed H. R. 3109 in December of 1902, but the Senate did not decide on the bill. The McCumber bill, entitled "Preventing the Manufacture or Transportation of Adulterated or Mis-Branded Food, Drugs or Liquors," did not include provisions requiring the Bureau of Chemistry to enforce the bill. Despite support from industry and reformers, the bills stagnated in Congress. By the end of the 58th Congress in March of 1905, neither Hepburn nor McCumber had prevailed in persuading Congress to pass their bills.

The combined support of the public, the executive office, and the medical profession expedited the passage a pure food and drug law. Media reports contributed significantly to achieving public support for these laws. The popular magazine *Collier's*, *The National Weekly* published a series of articles in late 1905 that exposed the dangerous content of many patent medicines that garnered great public support for

a pure food and drug law.³⁴ Similarly, Upton Sinclair's novel *The Jungle* generated public support for the law by exposing the repulsive and unsanitary practices of the meat packing industry.³⁵ In December of 1905, President Theodore Roosevelt appeared in Congress to present his ardent support of the passage of a pure food and drug bill, likely in direct response to these publications. Soon after, the AMA publically announced their support for regulating the drug industry.³⁶

Increased public support and awareness about the practices of the food and drug industry ensured the imminent passage of regulations of these industries. In January of 1906, Senator Weldon Heyburn from Idaho joined the efforts to pass food and drug regulations, introducing a bill that differed little from the original Hepburn bill. Heyburn's bill passed through the Senate and reached the House in the spring of 1906. The success of Heyburn's bill resulted largely from increased public support arising from the media exposés of 1905. Representative James Mann of Illinois played a large role in ensuring the passage of Heyburn's bill through the House. Legislative compromises included the Senate agreeing to require drug labels to include the presence of habit-forming drugs and the House agreeing to remove specific food standards. Both houses of Congress passed a bill regulating the food and drug industries in June of 1906. This bill was a hybrid of the original Hepburn bill

³⁴ Samuel Hopkins Adams, "The Great American Fraud," *Colliers, The National Weekly*, October 7, 1905.

³⁵ Upton Sinclair, *The Jungle* (New York: Doubleday, Jabber & Co, 1906).

³⁶ Thomas. A Bailey, "Congressional Opposition to Pure Food Legislation, 1879-1906", *American Journal of Sociology*, 36 (1930): 61; American Medical Association, *Digest of Official Actions, 1846-1958* (Chicago: The American Medical Association 1959), 184.

and the Heyburn bill from the Senate. President Roosevelt signed the Pure Food and Drugs Act into law on June 30, 1906.

Even though the public had supported the enactment of laws ensuring the purity and safety of drug products, the content of Congress' bills to regulate the industry regulated primarily the sale of these products. The enacted law differed little from the bill introduced by Colonel Hepburn in 1902. The Act did not prohibit the sale of dangerous products; it regulated only the labeling of food and drug products by prohibiting the sale of mislabeled or adulterated products.³⁷ The content of the 1906 Act demonstrates that Congress chose to enact regulations that treated drugs as commercial products. This initial law placed restrictions only on how drug manufacturers labeled drug products; it did not restrict how researchers developed drug products, how people used drug products, or how firms manufactured drug products.

Legislators built the private regulatory organizations in the federal regulations. They used the *USP* and the *NF* to define “drug products” in the Pure Food and Drugs Act, albeit not exclusively. While the AMA's Council on Pharmacy and Chemistry did not persuade legislators to regulate the development of drugs, legislators believed that the editors of the *USP* and the *NF* had established successful systems of identifying drug products. The Pure Food and Drugs Act defined a drug as any preparation contained in the *USP/NF* or any product “intended to be used for the cure,

³⁷ The 1906 Act banned food products that were “injurious to health”, but failed to do ban unsafe drug products.

mitigation, or prevention of disease.”³⁸ This distinction demonstrates that the legislative body understood that two types of drug products existed on the market. In using the *USP/NF* to define drug products, legislators set a precedent of using private organizations to regulate the drug industry that continues today. Despite Congressional debate, the Act authorized the BOC to enforce its statutes.

The Pure Food and Drugs Act responded to the lack of public information on food and drug products by instituting provisions that required the industry to increase the information available to consumers on the labels of their products. The Act prohibited the sale of adulterated and misbranded drugs in an attempt to prevent firms from falsely labeling their products. It defined adulterated products as those failing to fulfill the *USP* standards of strength, quality, and purity if the *USP* contained a monograph for that drug. However, the Act allowed firms to sell products that deviated from the *USP* standards if they stated the changes on the product’s label. This exception displays that the Act functioned mainly to ensure the truthfulness of drug product labels, rather than to markedly change the products themselves. The Act defined misbranded drugs as those whose labels included false or misleading statements about a product’s content or quantity. The Act also mandated that firms selling products containing “alcohol, morphine, opium, cocaine, heroin, alpha or beta eucaine, chloroform, cannabis indica, chloral hydrate, or acetanilide, or any derivative,” must include those compounds on the labels of those products.³⁹ This

³⁸ “The Pure Food and Drugs Act,” Public Law 384, *U.S. Statutes at Large*, 34 (1906) 768-771.

³⁹ “The Pure Food and Drugs Act”.

clause became important, as it dissuaded firms from using these compounds in their products unnecessarily.

Using Standardized Scientific Methods to Produce Drug Products

Enforcing the Pure Food and Drugs Act: The FDA in the 1910s and 1920s

Despite the industry's concerns during the bill's passage, the 1906 Act had a minimal impact on the on the content of drug products. The Act caused firms to reduce their usage of opiates and alcohol in drug products because it required them to include these ingredients on their labels, but firms did little else to change the content of their products. With the reduced use of these dangerous additives, the greatest danger of patent medicines became their use over more legitimate remedies, rather than their usage alone. The Act prevented firms from making outlandish claims about the contents of products, which compelled firms to consider the labels they used on their products and the words they used to describe their products more critically.

Although legislators banned the sale of adulterated drug products in the 1906 Act, the definition of "adulterated" referred only those drugs included in the *USP* or *NF* that differed from the official standard.⁴⁰ Any drug not included in those private publications could not be considered adulterated under the law, even if consumers or physicians found the product to be unsafe or lethal.

⁴⁰ Although the *USP* did not specifically list drug products by their firms, the law defined any products sold under the name of a drug compound in the *USP* as a drug. See Jeremy Greene and Scott Podolsky, "Keeping Modern in Medicine: Pharmaceutical Promotion and Physician Education in Postwar America," *Bulletin of the History of Medicine* 83, no. 2 (2009): 331-377.

After 1906, the BOC established a successful system for collecting and analyzing food and drug products that remains at the core of enforcing food and drug regulations today. The BOC established procedures for inspecting the practices of drug companies at their manufacturing facilities and for analyzing the chemical content of these products. They informed federal prosecutors of the existence of those products they believed violated the Act, who then decided which cases to prosecute. In the 1910s and 1920s, the Act had a winning record in court. However, this likely speaks more to the success of the BOC than the ingenuity of the Act. The low fines created by the Act prompted many manufactures to choose to pay the fines rather than manage a court case when accused of selling illegal products.⁴¹ . In 1927 the Bureau of Chemistry became part of the newly created Food, Drug and Insecticide Administration. Three years later this office became the Food and Drug Administration (FDA), which continued to enforce food and drug regulations today.

In 1912 Congress passed the first amendment to the Pure Food and Drugs Act, the Sherley Amendment. This amendment attempted to tighten regulations on the patent medicine industry by prohibiting drug product labels from including false therapeutic claims. However, during Congressional debates opponents of the amendment changed the language of the legislation so that it prohibited only false therapeutic claims that attempted to defraud to the purchaser. Attempting to prove a manufacturer's intent to defraud created a substantial amount of extra work for the

⁴¹ Daniel, Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010).

BOC in prosecuting firms for mislabeling drug products. Practically, this amendment did little to prevent firms from making false therapeutic claims.

The law did not remove many drug products from the market and the ethical drug industry and the proprietary medicine industry continued to grow throughout the 1910s and 1920s. During this time, physicians and the public consistently depended on the use of pain relievers (aspirin), sedatives (opiates) and emetics (ipecac) to treat human ailments. Both ethical drug and patent medicine firms marketed countless drug products containing these drug compounds. Although these compounds could treat some ailments, they could not treat infectious diseases, the most serious threat to American health in the first half of the twentieth century. The public wanted drug products that could treat diseases like tuberculosis, smallpox, syphilis, polio, and influenza. Today, effective antibiotics have reduced the prevalence and mortality rates of infectious diseases to an extent that obscures the extreme lethality of these diseases in the past. A great deal of proprietary medicines sold in the 1910s and 1920s claimed to cure infectious diseases, but very few of these agents truly affected infectious pathogens.

Developing Effective Anti-Infective Agents

The number of medical researchers using rational, scientific methods to develop drug products increased steadily in the first decades of the twentieth century. By the 1910s, medical researchers began discovering and synthesizing increasingly effective anti-infective compounds. These researchers employed new scientific knowledge of the chemistry and of the human body to find compounds that could reduce the severity of infections. In 1910 Paul Ehrlich's laboratory in Germany

discovered arsphenamine, the first drug compound found to diminish bacterial infections in humans. Ehrlich was a chemist who performed numerous assays to test the ability of specific chemical compounds to inhibit bacterial growth. Soon after this discovery, German drug manufacturers began selling a drug product called Salvarsan, containing arsphenamine, in both in Europe and in America. Physicians could not use Salvarsan to treat many diseases, but they did use it to treat numerous cases of syphilis. Salvarsan was the anti-infective agents on the drug market and was embraced by physicians and the public.⁴²

Also in Germany in the early 1910s, chemists found that a class of compounds called the sulfonamides could kill bacteria without harming animal tissue and discovered the potential therapeutic value of these compounds.⁴³ For three decades, chemists and bacteriologists endeavored to identify specific therapeutically useful sulfonamide compounds.⁴⁴ By the 1930s, the sulfonamide compounds became the first major class of effective anti-infective agents used consistently by medical practitioners. The development of sulfonamide drug products represents the first major efforts to deliberately test analogs of a specific compound for therapeutic value using *in vitro* assays, animal testing, and clinical experimentation on humans. Researchers from various countries communicated throughout the 1920s and 1930s concerning the therapeutic value of sulfonamide compounds.

⁴² John Parascandola, "Alkaloids to Arsenicals: Systematic Drug Discovery Before the First World War," in *The Inside Story of Medicines: A Symposium*, ed. by Gregory J. Higsby and Elaine C. Stroud (Madison, WI: American Institute of the History of Pharmacy, 1997), 78.

⁴³ Perrin H. Long and Eleanor A. Bliss, *The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds*, (New York: The Macmillan Company, 1939), 3.

⁴⁴ Long and Bliss, *The Clinical and Experimental Use of Sulfanilamide*, 1-11.

In the early 1930s, medical researchers in Germany, France, England, and America endeavored to develop drug products using the sulfonamides. By the end of 1936, American researchers had demonstrated the effectiveness of the compound sulfanilamide (para-amino benzene sulfonamide) in treating human infections using clinical trials. The AMA Council on Pharmacy and Chemistry accepted sulfanilamide into *New and Nonofficial Remedies* in July of 1937.⁴⁵ Physicians used sulfanilamide products to treat staphylococcal and gonococcal infections, urinary tract infections, gas gangrene, and other bacterial infections. The discovery of sulfanilamide exemplifies the drug industry's increasing reliance on scientific experimentation to develop products. By 1937 firms sold both pure sulfanilamide products (ethical drugs) and compounded products containing sulfanilamide and a mixture of other compounds (patent medicines). The fact that any company could purchase sulfanilamide to create and market a drug product as a cure for infections ultimately convinced legislators to begin regulating how firms used scientific techniques to develop drug products.

While the use of isolated chemical compounds as therapeutic agents began in the early nineteenth century, the extensive use of chemical and clinical experimentation to determine potential therapeutic value of these compounds began in the 1930s. Researchers used a range of techniques to better determine the chemical effects of a single compound. These technological developments began to standardize the procedures and experimental designs used by researchers to develop drug products, which would continue through the 1950s. This standardization allowed

⁴⁵ Long and Bliss, *The Clinical and Experimental Use of Sulfanilamide* 10.

researchers to more easily build upon knowledge gained in past experiments and promoted academic collaboration.

Encouraging Regulatory Change: The Elixir Sulfanilamide Tragedy

The sulfanilamide products on the market in 1937 varied immensely in strength, content, and toxicity. Patent medicine companies that lacked the resources to perform clinical trials, animal testing, and other chemical analyses began creating products with the sulfonamides in addition to those already sold by ethical drug firms. The production of one sulfanilamide product by a manufacturer who traditionally sold proprietary medicines demonstrates the concrete negative effects that resulted from drug regulatory system that controlled only the labeling of drug products. This product, sold by the S. E. Massengill Company and known as “Elixir Sulfanilamide”, killed almost one hundred people because it contained a lethal additive.

Massengill, based in Tennessee, wanted to create a sulfanilamide product in liquid form. Roland Sherman, an FDA Food and Drug Investigator, claimed that popular opinion in the American South in the 1930s held that, “if you can't give colored people or children a red liquid medicine, you aren't any kind of a doctor at all.”⁴⁶ Chemists at the company discovered that sulfanilamide would not dissolve in common solvent like water and alcohol.⁴⁷ The high demand for a more palatable, flavored liquid sulfanilamide and the company’s desire for profit pressured

⁴⁶ Roland Sherman, oral history by Robert Porter, The FDA Oral History Series, July 4, 1978, The FDA History Office, Rockville, MD, 5. Such stereotypes about the preferences of medicine form for different geographical areas proliferated during this era when the promotion of drug products could be easily tailored to a given market. An article in *Time* reported that Southerners preferred their medicine in liquid form while New Englanders were partial to pills (“Fatal Remedy,” *Time* November 1, 1937, 61).

⁴⁷ “Post-Mortem,” *Time* December 20, 1937, 48-49.

Massengill chemists to quickly find a solvent for the compound. Unfortunately, the substance in which they chose to dissolve sulfanilamide, diethylene glycol, is highly toxic to humans. Presumably, the chemists at Massengill had not spent many years developing drug products, and were not accustomed to considering toxicity when attempting to dissolve solids in liquids. When the chemists realized that sulfanilamide does not dissolve in water or alcohol, they resorted to using an all-purpose solvent in chemical labs, diethylene glycol, without considering its potential toxicity. The Massengill Company's protocol held that the chemists must perform tests on taste and appearance of the drug, but did not require safety testing on animals or humans. The chemists at Massengill failed to do any safety testing on Elixir Sulfanilamide before releasing shipments in September of 1937. At least seventy, and probably over one hundred, people died as a result of taking Elixir Sulfanilamide.⁴⁸ Since sulfanilamide was one of the first successful antibiotics on the market, doctors prescribed Elixir Sulfanilamide frequently once it became available. Doctors wrote the majority of the prescriptions for the use of Elixir for the treatment of gonorrhea, kidney infections, and other upper respiratory staphylococcal infections.

The company used scientific principles in developing the product, but not to establish the safety or effectiveness of the product as a therapeutic. As a result of the Elixir deaths, reformers and Congressmen began to call for an amendment to the FDCA that would require companies to prove the safety of drug products before they could sell the products legally. One may be quick to blame the profit-hungry company for skirting the rules and causing these deaths, but the Massengill Company

⁴⁸ Carpenter, *Reputation and Power*, 85-89.

broke only one minor clause of the 1906 Pure Food and Drugs Act. The law specified that any product labeled as an “elixir” must contain alcohol, and the Elixir Sulfanilamide did not contain alcohol. The FDA managed to repossess and destroy most of the product from pharmacists by charging the Massengill Company with misbranding only because of this infraction.

Most narratives of the history of the FDA and drug regulations label the Elixir incident as distinctly causative of the forthcoming Food, Drug and Cosmetic Act of 1938. This categorization, however, disregards the importance of the class of sulfonamide drugs and the complicated identity of the Elixir Sulfanilamide as a product of both the ethical drug industry and the proprietary medicine industry. The Massengill Company perceived a market for a liquid sulfanilamide so they bought the raw product and found a solvent in which to sell their own product. The deaths displayed the potential dangers of allowing drug manufacturers to become reckless and hasty in developing drugs.

Firms’ inclination to respond to consumer desires caused developers of drug products in the 1930s to sometimes disregard contemporaneous scientific knowledge. By 1937, scientists knew that ethylene glycol, a compound closely related to diethylene glycol, was a dangerous poison. Investigations by the FDA and other academic scientists concluded that diethylene glycol was the poisonous substance in Elixir Sulfanilamide. After the Elixir deaths, many researchers believed that the toxicity of diethylene glycol could have easily been predicted because of the known danger of ethylene glycol.⁴⁹

⁴⁹ “Fatal Remedy,” *Time* November 1, 1937, 61.

The media covered the Elixir deaths heavily and portrayed the event as a national tragedy, fueling popular support for new drug regulation. In the book *Reputation and Power*, political scientist Daniel Carpenter thoroughly describes the media coverage of these events and attributes the lasting effects of the tragedy to the media's portrayal of the events.⁵⁰ While I support Carpenter's analysis, the fact that this product was legal under the current law illustrates why physicians, legislators, and reformers discerned a need for new food and drug legislation in the early 1930s. The scandal surrounding the Elixir deaths expedited the passage of legislation to amend the 1906 Act. The Elixir represents both the new scientific successes in developing drug products and the practices of the profit-driven patent medicine industry. The widespread use of the sulfa drugs by physicians and patients in the 1930s prompted legislators to consider amending the Pure Food and Drugs Act by convincing them that the drug products could be effective. While the Elixir events specifically prompted legislators to require firms to use scientific assessments to prove the safety of the drug products they sold, the sulfa drugs, as the first effective anti-infective products, prompted legislators begin considering tightening regulations on the drug industry to encourage the practices of the ethical drug industry

Implementing Stronger Food and Drug Regulations: 1933-1938

The Public Concern with the Safety of Drug Products in the 1930s

Within three years of its passage, members of the medical community, health reformers, and consumer advocates began calling for amendments to the Pure Food

⁵⁰ Carpenter, *Reputation and Power*, 85-112.

and Drugs Act.⁵¹ They believed the Act did not protect consumers from harmful products or adequately punish offenders. After the passage of the Sherley Amendment in 1912, Congress amended the 1906 Act five more times to clarify definitions within the text.⁵² These amendments, though, had few tangible effects on the Act's regulation of the food and drug industries. In the late 1920s and early 1930s reformers worked to increase the American public's awareness of defects in the current food and drug legislation. The group Consumers' Research played a large role in advocating for consumer rights during the first half of the twentieth century.⁵³ Two members of the group, Arthur Kallet and Frederick J. Schlink, authored a book entitled *100,000,000 Guinea Pigs: Dangers in Everyday Foods, Drugs and Cosmetics*. They argued that food, drug, and cosmetics manufacturers sold their products as part of a large experiment on the American public. They also claimed the experiments aimed to assess the toxicity of poisons and had shortened the life span of the average American by three to ten years. The book advocated for changes in the current "feeble and ineffective" food and drug legislation, claiming that the laws did not prevent manufacturers from defrauding and endangering the public.⁵⁴

FDA officials assembled an exhibit displaying the dangerous and unsanitary food and drug products legal under the current Pure Food and Drugs Act using the

⁵¹ *Digest of Official Actions, 1846-1958: The American Medical Association*, 185.

⁵² "Federal Food Drug and Cosmetic Act with Amendments," compiled by Gerard Walsh, Jr., (Washington, D.C.: US Government Printing Office, 1981), 1-7.

⁵³ "The American Chamber of Horrors," *Histories of Product Regulations*, U.S. Food and Drug Administration, accessed January 9, 2012, <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/ucm132791.htm>.

⁵⁴ Arthur Kallet and Frederick J. Schlink, *100,000,000 Guinea Pigs: Dangers in Everyday Foods, Drugs and Cosmetics*, (New York: The Vanguard Press, 1932), 4-10.

content of *100,000,000 Guinea Pigs*. The FDA originally arranged the exhibit to educate Congressmen. The exhibit, colloquially known as “The American Chamber of Horrors”, displayed the need for laws preventing deceptive packaging and standardizing food labeling. The exhibit also traveled around the country to public spaces where FDA employees could educate the public. The exhibit demonstrated the need for new food and drug legislation to Congress and the American people. The displays in “The Chamber of Horrors” emphasized the mislabeling and adulteration of food, more so than that of drugs. FDA investigators also spent more time analyzing mislabeled or adulterated food products than drug products in the 1930s.⁵⁵ The immediate manufacturing faults of the food industry provided better fuel for increasing popular and legislative support for a new statute than did the issues of the drug industry. However, worries about the safety of drug products and the Elixir deaths ultimately prompted change to federal food and drug law.

Debating a New Food and Drug Law: Legislative History

Legislators began to move towards revising the Pure Food and Drugs Act during Franklin D. Roosevelt’s New Deal program of reform in the early 1930s. The public elected Franklin D. Roosevelt during the greatest depression in American history, when unemployment levels had reached over twenty percent of the population. From 1933 through 1936, the Roosevelt administration implemented reforms aiming to improve the American economy. These New Deal reforms aimed to aid large corporations and promote commodity production as a source of employment.

⁵⁵ Sherman, 3-10.

Roosevelt appointed Rexford Tugwell as the new Assistant Secretary of the USDA in 1933.⁵⁶ Tugwell believed in the comprehensive use of federal power to regulate American industry. He played a role in creating many major New Deal administrative boards, including the Agricultural Adjustment Administration (AAA). The AAA raised the cost of agricultural goods by paying farmers to destroy crops, which decreased their supply.⁵⁷ Tugwell also promoted increased regulations on the food and drug industries. FDA Chief Walter Campbell entered into discussions with Tugwell concerning the deficiencies the body's regulatory power in 1933.⁵⁸ The FDA strongly supported a new, stronger food and drug legislation, but few Congressmen wanted to sponsor a bill that would inevitably produce controversy.⁵⁹ Eventually, Tugwell enlisted Senator Royal S. Copeland, a Democrat from New York, to lead the Congressional campaign to amend the Pure Food and Drugs Act. As the former Health Commissioner of New York City, Copeland clearly held authority in the field of food and drug legislation. However, many consumer advocates objected to

⁵⁶ Shayne C. Gad, *Regulatory Toxicology*, 2nd ed., (New York: Taylor and Francis, 2001), 11-14.

⁵⁷ Alan Brinkley, *The Unfinished Nation: A Concise History of the American People*, Volume II, (New York: McGraw-Hill Inc., 1993), 697.

⁵⁸ Most of this legislative history has been sourced from a piece written immediately after the Act's passage in 1938 by David Cavers in the journal *Law and Contemporary Problems*. Cavers was a member of the original committee assembled by Tugwell to rewrite the Pure Food and Drugs Act and acknowledges his bias in favor of the bill and its legislators.

⁵⁹ Charles O. Jackson, *Food and Drug Legislation in the New Deal* (Princeton, NJ: Princeton University Press, 1970), 24-29.

Tugwell's choice because Copeland had given radio talks for a program sponsored by a patent medicine.⁶⁰

Regardless of this disapproval, Copeland drove the new food and drug law through Congress from 1933 until its passage in 1938. The AMA, the ethical drug industry, and many public health employees strongly supported Copeland during this Congressional battle. Five different proposed bills surfaced during this debate. The first four of these bills, proposed in 1933, 1934, and 1935, contained very similar content. These bills retained the structure of the 1906 Act, but defined "adulterated" and "misbranded" more thoroughly than the old law. If enacted, these bills would have regulated the sale of drugs more strictly, but would not have regulated any other aspect of the drug production process significantly. After the Elixir events, Copeland introduced a fifth bill, which included a section that would regulate the development of drug products. Congress passed this bill in June of 1938.

The bills that Copeland introduced into Congress in 1933 and 1934 maintained the structure of the Pure Food and Drugs Act in that they were grounded in the prohibition of the sale of misbranded and adulterated foods and drugs. In 1933 Tugwell assembled a group of FDA employees, academic scientists, and state health officials to revise the Pure Food and Drugs Act. Because of the scale of the planned changes, the group agreed to write a new act, rather than attempt to amend the 1906 Act.⁶¹ Tugwell's group met with representatives from the food and drug industries, but ultimately relied upon their collective experience and expertise in the public

⁶⁰ Charles O. Jackson, "The Ergot Controversy: Prologue to the 1938 Food, Drug and Cosmetic Act," *Journal of the History of Medicine and Allied Sciences*, 23 (1968): 257; Cavers, "The Food, Drug and Cosmetic Act," 2-10.

⁶¹ Cavers, "The Food, Drug and Cosmetic Act," 6.

health field to produce a final bill. The group authored a bill that Copeland introduced it into the Senate in late 1933 as S. 1944. Congressmen and the media referred to the proposed bill as the “Tugwell Bill” which placed the bill firmly in line with New Deal ideals.⁶² The name gave the bill a distinct political association, even though President Roosevelt remained mostly silent on the issue. S. 1944 included provisions that would have increased the extent to which the government could use scientific testing in judging the legality of drug products. These included clauses requiring firms to identify the entirety of a drug product’s contents on its label, requiring the government to create its own tests for assessing the purity of the contents of drug products, and prohibiting the sale of products containing unsanitary ingredients.⁶³

Congress did not pass S. 1944 in 1933. While the drug industry opposed the passage of S. 1944 most strongly, consumer advocates and health reformers also disapproved of the bill. Reformers believed the bill did not propose to regulate the industries strongly enough and the industries did not want to be further regulated. S. 1944 did not directly prohibit the sale of unsafe drug products. An ongoing battle between the Federal Trade Commission (FTC) and the Food and Drug Administration over control of advertising of foods, drugs and cosmetics also weakened the bill’s potential Congressional success. The bill would have authorized the FDA to enforce restrictions on food and drug advertising, a power then held by the FTC.

⁶² “Medicine Curb Held Hardship: Tugwell Bill Called Harm to All Legitimate Remedy Makers,” *The Washington Post*, October 7, 1933, 7; “Impending Laws Cloud Ad Outlook: Tugwell Bills Retard Programs of Food and Drug Stories, Executives Claim,” *The New York Times*, November 12, 1933.

⁶³ Cavers, “The Food, Drug and Cosmetic Act,” 22-30.

Throughout the legislative debates of the 1930s, Copeland and his supporters maintained the need to include provisions in the bill that would allow the government to use scientific assessments to monitor the contents of drug products. The regulations that Congress enacted in 1938 included many, but not all of the provisions of S. 1944. Congress retained the sections of S. 1944 that allowed for the regulation of therapeutic devices and broadened the definition of a drug to include substances intended merely to affect the structure or function of the body, in addition to those intended to treat disease.⁶⁴ Congress also retained the sections of S. 1944 that required firms to label drug products with a list of all active ingredients, directions for use, and “Warning-May be Habit-Forming” for products containing a list of narcotic and hypnotic compounds.⁶⁵ S. 1944 would have defined any drug as misbranded “if ‘its labeling bears any representation, directly or by ambiguity or inference, concerning the effect of such drug which is contrary to the general agreement of medical opinion.’”⁶⁶ Although this clause theoretically would have eliminated ineffective drug products from the market, its practical use likely would have proved difficult. In 1933 medical professionals rarely came to consensus about therapeutics. This clause indicates that the FDA leaders and legislators recognized the divide between effective and ineffective drugs, as perceived by the scientific medical community. They valued the medical, and implicitly scientific, opinion. AMA leaders supported the passage of Copeland’s bill and called for additional labeling requirements and a clause mandating physician’s prescriptions for some drugs.

⁶⁴ Cavers, “The Food, Drug and Cosmetic Act”, 11.

⁶⁵ Cavers, “The Food, Drug and Cosmetic Act,” 31-42.

⁶⁶ Cavers, “The Food, Drug and Cosmetic Act,” quotation on 34.

The same committee that wrote S. 1944 reconvened and produced another bill that Copeland presented to Congress in January of 1934, numbered S. 2000.⁶⁷ The hearings on this bill generated numerous changes to the text; Copeland introduced a new bill incorporating these changes in February, S. 2800. This bill included many of the new definitions of S. 1944 and would have given the FDA the power to make multiple seizures of the same product. Disputes over federal advertising authority, the right to self-medication, the power of the FDA to make multiple seizures, and the amount of poisons in food necessary for a product to be considered adulterated dominated both the House and Senate discussions about S. 2800 in 1934.⁶⁸ Congress did not pass S. 2800 in 1934 and Copeland introduced another similar bill in January of 1935, S. 5.

Throughout the Congressional debates over Copeland's bills, disagreements over the body that would gain the authority over restricting food and drug advertising prevented the passage of new food and drug regulations. In 1914 Congress passed the Federal Trade Commission Act. This Act gave the Federal Trade Commission the sole power to enforce restrictions on the advertising of food and drug products, albeit minimally.⁶⁹ FTC leaders believed that power should remain with their Commission. The FDA hoped to gain control over food and drug advertising and to increase the stringency of their regulation. The original S.1944 bill, and the subsequent S.2000

⁶⁷Cavers, "The Food, Drug and Cosmetic Act, 15.

⁶⁸ The issue of poison levels in foods stemmed from the difficulty of removing pesticides, like lead and arsenic, from produce. The law stipulated a great reduction in the amounts of these pesticides that could remain on the produce when it reached the market.

⁶⁹ "FTC's History Timeline," Federal Trade Commission, accessed December 10, 2011, <http://www.ftc.gov/ftc/history/ftchistory.shtm>.

(1934), S. 2800 (1934) and S. 5 (1935) all included provisions that empowered the FDA to control food and drug advertisements. Numerous Congressmen opposed this delegation of power. The Senate passed S. 5 in May of 1935 and again in March of 1937. On both occasions the House refused to pass a bill giving the FDA power over advertising regulation and the bill stagnated in Congress.⁷⁰

In 1937 Senator Burton Wheeler of Montana and Representative Clarence Lea of California proposed a bill to amend the FTC Act. Lea and Wheeler led a large portion of the opposition to Copeland's measures because of the advertising regulation. They decided to write a clause that directly authorized the FTC to regulate the advertising of food, drug, and cosmetics in the amendments of the FTC Act. After considerable debate the bill passed through both houses and the Wheeler-Lea Act Roosevelt signed it into law in early 1938.⁷¹ The amended FTC Act empowered the FTC to enforce the prohibition false advertising of foods, drugs, and cosmetics. This forced Copeland to remove the section of S. 5 that gave the FDA similar powers. Just as the passage of the FTC became evident, the Elixir Sulfanilamide incident struck America, thrusting the work of the FDA and the current food and drug law debate into the public eye.

Debating New Regulations in the Context of the Elixir Deaths

The deaths that resulted from Elixir Sulfanilamide directly caused Copeland to change the content of the bills that he had proposed to regulate food and drug products. Until the incident occurred in the fall of 1937, the majority of the changes concerning drug regulation between the amended 1906 Act and the proposed bills

⁷⁰ Cavers, "The Food, Drug and Cosmetic Act, 16-18.

⁷¹ "FTC's History Timeline".

rested in modifications to the definitions of “mislabeled” and “adulterated” drugs. These changes chiefly would have required firms to label drug products with directions for use, a list of all ingredients, and the specific quantity and strength of its drug compounds. After the abatement of the Elixir Sulfanilamide crisis, FDA Chief Walter Campbell authored a report detailing the legislative changes required to avoid another drug incident. The report convinced Copeland to include a pre-market drug approval process in his newest bill, S. 3073 (1938).⁷² Copeland did so by adding an entire section to the bill entitled “New Drugs”. The section would require firms to submit an application before marketing new drug products that proved the products were “safe for use under the conditions of use” specified on their labeling.⁷³ The “New Drugs” section would not have been included in the bill without the occurrence of the Elixir Sulfanilamide deaths.

The AMA’s Seal of Approval Program and the work of the AMA’s Council on Pharmacy and Chemistry provided a precedent for this type of pre-market approval system. Copeland did not cite this Program as causative of the inclusion of the “New Drugs” section. However, the inclusion of the pre-market approval system represents another example of how the regulation of drugs by private organizations provided foundation upon which Congress enacted public regulations. After 1938, these organizations began to lose direct regulatory power because the state began controlling the industry more strictly. Congress continued to use the *USP* and the *NF* to define quality and purity standards for drug products.

⁷² Carpenter, *Reputation and Power*, 95-102.

⁷³ Cavers, “The Food, Drug and Cosmetic Act, 40; “Federal Food Drug and Cosmetic Act with Amendments,” 24-25.

The therapeutic success of sulfonamide products encouraged the organized medical profession supported legislation that would promote the production of equally effective products. The increased authority of the medical profession during this time meant that their support affected Congress' writing of the new drug regulatory bills. The AMA publically declared support for the Copeland bill and instructed all state medical associations to work towards the passage of a new food and drug bill.⁷⁴ The support of the medical profession, along with the extreme public outcry over the Elixir Sulfanilamide deaths propelled Copeland's bill through Congress in 1938. Copeland collaborated with Representative Virgil Chapman of Kentucky who had authored a similar bill, H. R. 9341, to revise S. 5. The two urged Congress to expedite the passage of the bill.

After some continued debate, both houses passed S. 5. President Roosevelt signed the Federal Food, Drug and Cosmetic Act into law on June 25, 1938. In doing so he nullified the 1906 Act and ended the five-year battle over new food and drug legislation. The FDCA retained the structure of the Pure Foods and Drugs Act by prohibiting mislabeled or adulterated food and drug products. Moreover, the Act added a section on new drugs and expanded its regulatory scope to include medical devices and cosmetics. The law prohibited the sale of drugs without instruction for use, without warnings for dangerous chemicals, and those containing substances injurious to health. The pre-market approval process affected the future of drug production more so than any other provisions of the FDCA by giving the FDA power

⁷⁴ *Digest of Official Actions*, 189-190.

to prevent the sale of a product before it reached consumers⁷⁵. Ultimately, the passage of the 1938 Act responded to the demands of the FDA, consumer advocates, and medical professionals to tighten the regulations governing the sale of foods and drugs in America.

The law established a system that promoted the use of scientific experimentation, and specifically clinical trials on humans, to develop drug products and ensure their safety. The “New Drugs” section of the FDCA introduced a system of regulating drugs already in place for vaccines. The 1902 Biologics Control Act already required clearance by the USDA before the marketing of vaccines. The acceptance of that measure by biologics manufacturers and health reformers inspired USDA officers to advocate for same procedure for drug products.⁷⁶ The FDCA also exempted “drugs intended solely for investigational use by experts qualified by scientific training and expertise” from the labeling restrictions of the bill.⁷⁷ This created a class of “investigational drugs” that firms could distribute to physicians to perform clinical trials. Although the law did not specify how firms should perform clinical trials, Congress provided that firms could do so legally as a means to establish the safety of drug products.

Senator Copeland worked closely with FDA Chief Walter Campbell in creating a bill that reflected the views of the FDA on food and drug regulation.⁷⁸ The demand for scientific evidence for the safety of drug products originated directly from

⁷⁵ See Appendix A for a complete list of documents included in a New Drug Application, as required by the 1938 law.

⁷⁶ Carpenter, *Reputation and Power*, 102.

⁷⁷ “Federal Food Drug and Cosmetic Act with Amendments,” 25.

⁷⁸ William Goodrich, oral history by Ronald Ottes and Fred Lofsvold, The FDA Oral History Series, October 15, 1986, 4-5.

the Elixir event. The original Tugwell bill from 1933 included a clause that would have prohibited the use of therapeutic claims on drug product labels without sufficient medical endorsement. This would have required firms to prove drug efficacy claims in order to include them on the labels of products. However, Congress removed this clause in response to industry opposition. The initial inclusion of this clause indicates that Copeland and reformers believed in the need for scientific analysis of drug products to ensure their merit before the Sulfanilamide incident. The expansion of scientifically developed therapeutics and the emergence of the sulfa drugs elicited these beliefs.

The growth of scientifically based drug design fragmented the drug industry into two categories, patent medicines and ethical drugs, which a single piece of legislation, the Pure Food and Drugs Act, could not simultaneously regulate. Congress chose to enact regulations that further compelled patent medicine makers to adopt the scientific practices of the ethical drug industry. Specifically, Congress pressured all drug makers to perform scientific clinical experiments to determine the safety of their products and to perform chemical assays to determine the contents of their products. In passing the FDCA, Congress established scientifically based assessments and gatekeeping procedures to regulate the sale and development of drug products.

Conclusion

Private organizations regulated the drug industry before the enactment of public food and drug regulations in 1906. These private regulatory organizations

provided Congressmen and the Bureau of Chemistry with a precedent for monitoring drug products that emphasized scientific analysis. Congress used these organizations to define drug products legally. Furthermore, the events surrounding and the public response to the commercial success products on the drug market in the 1900s, the sulfonamides, and the Elixir impacted the creation and passage of legislation regulating the industry. The Elixir Sulfanilamide deaths and the media coverage of the event prompted the inclusion of the pre-market approval process for new drugs in the FDCA by demonstrating the negative effects of an unregulated system. However, the structure of the New Drug Application (NDA) process originated from the process used by the AMA's Council on Pharmacy and Chemistry in determining the drugs included in *New and Nonofficial Remedies*. The private bodies regulating drugs in the nineteenth century approved of the use of scientific experimentation in developing, analyzing, and evaluating drug products. In following the precedent of private bodies regulating drug products, legislators indicated that the state recognized scientific experimentation as crucial to the drug development and analysis process.

The Bureau of Chemistry and the FDA developed a system of investigating drug products that employed chemical, bacteriological, pharmacological, and biological analyses. Scientific knowledge in these fields expanded during the 1920s and 1930s. Academic and commercial drug developers used this knowledge in creating and testing drug products. Correspondingly, the content of the FDCA more extensively depended on scientific experimentation and firmly favored the ethical drug industry than did that of the 1906 Act. Despite the increased use of scientific principles to regulate drug products, market pressures continued to affect the

production decisions of drug manufacturers throughout the first four decades of the twentieth century, as shown by the deaths resulting from Elixir Sulfanilamide.

The enactment of the Pure Food and Drugs Act in 1906 arose out the Progressive-Era emphasis on implementing legal reforms to ensure society's health. The variety of products on the market compelled legislators to standardize the labeling practices of the industry. The shift towards scientifically developed drugs in the early 1930s, as indicated by the success of the sulfa drugs, prompted legislators to revise the 1906 Act. In enacting the FDCA, legislators reshaped the drug industry by compelling firms to use scientific principles to establish the safety of their products. While the 1906 Act regulated only the sale of drug products, the FDCA regulated both the sale and development of drug products. Even though the FDA struggled to maintain a consistent and rigorous system of reviewing NDAs, the law introduced the system of premarket approval for drug products.

The diversity of drug products on the market in the early 1900s and the therapeutic and commercial success of the sulfa drugs in the 1930s prompted Congress to enact federal drug regulations. Similarly, new classes of drugs in the 1940s impacted how the FDA enforced these regulations. These included stronger anti-infective agents, cardiovascular agents, and cancer therapeutics. The next chapter discusses the enforcement of the 1938 Act and the role of World War II in shaping the pharmaceutical industry in the 1940s and 1950s. Congress amended the FDCA in the 1940s to expand its regulatory authority to the manufacturing and use of drug products. In doing so, Congress reacted to the success of new antibiotics, namely penicillin and streptomycin.

Just as the FDCA strengthened the provisions of the 1906 Act regulating the sale of drug products, further amendments to the FDCA strengthened the provisions of the FDCA regulating the development of drug products. The introduction of new drug categories and specific drug products elicited these amendments in the 1940s, 1950s, and 1960s.

Chapter Two: Regulating the Manufacture and Use of Drug Products: 1939-1951

Introduction

The FDA hired dozens of field inspectors, lawyers, medical officers, and administrators following the passage of the FDCA in order to handle its increased workload.⁷⁹ The FDA's New Drug Division employed only three medical officers from 1939 until the mid-1950s.⁸⁰ This suggests that the certification of new drug products did not dominate the activities of the FDA in the 1940s. In practice, the FDA mainly regulated the sale of drug products in the early 1940s. However, by 1951 Congress had amended the FDCA to regulate drug sale, manufacture, and use. After the Federal Food, Drug and Cosmetic Act became effective in 1939, FDA employees worked to compel the growing drug industry to comply with the new regulations. This chapter details how the FDA enforced the FDCA in the years immediately following its passage. By this time, the scientifically based practices of the AMA and the *USP* editors had become the standard for the FDA and ethical drug firms in developing and assessing the merit of drug products.

The first amendments to the FDCA, the Penicillin and Insulin Acts implemented certification programs for the manufacturing of those drugs. These programs aimed to ensure consistency in safety, efficacy, and strength of drug

⁷⁹ Goodrich, 125-129; Ralph Smith, Arthur Checchi, Gilbert Goldhammer, et al, oral history by James Harvey Young, Richard McFayden, and Terrance, Gough, The FDA Oral History Series, June 30, 1978, The FDA History Office, Rockville, MD.

⁸⁰ Smith, Checchi, Goldhammer, 1-10.

products by requiring that the FDA certify all batches of penicillin and insulin drug products. The Durham-Humphrey Amendment of 1951 legally differentiated between drugs that could be sold by prescription-only and those sold over-the-counter (OTC). This was the first amendment that prevented the public from purchasing certain drugs (prescription-only drugs). With this amendment, legislators recognized the authority of the licensed physician in using drug products effectively.

The number of new drugs introduced into the American market increased yearly throughout the 1940s and 1950s.⁸¹ Firms produced increasing amounts of anti-infective agents, hormone drugs, and cardiovascular regulating agents every year in the 1940s.⁸² In 1944 the FDA issued a report stating that their medical officers judged the therapeutic merit of a drug product based on its safety and efficacy. During World War II, the government sponsored research on the development of penicillin as a drug product. The government's efforts influenced how researchers performed clinical trials and the extent to which pharmaceutical companies could produce drugs on a massive scale. During the war, researchers also developed methods of performing controlled clinical trials and developed techniques for producing large amounts of drug products. These procedures became part of the scientific standard for developing drug products in the late 1940s and early 1950s.

The antibiotics penicillin and streptomycin were the first major drugs that could cure diseases rather than simply treat them. Penicillin could cure pneumonia and streptomycin could cure tuberculosis, but if patients used the right dosages and

⁸¹ Paul de Haen, "Compilation of New Drugs 1940 thru 1975," *Pharmacy Times* 42 no. 3 (1976): 40-74.

⁸² de Haen, "Compilation of New Drugs 1940 thru 1975," 40-42.

correct frequency. Although the sulfa drugs of the 1930s effectively treated a number of infectious diseases, they could not completely eliminate the bacterial source of disease. As it became clear that penicillin and streptomycin could cure infectious diseases, researchers, FDA officials, and eventually legislators came to believe that these drug products needed to be manufactured and used correctly to ensure their consistent effectiveness. Since the FDCA regulated only the sale and labeling of drugs, legislators would have to amend the Act to allow the FDA to regulate the use and mass manufacture of drug products.

In this chapter I argue that the discovery and commercial success of effective drugs, namely the antibiotics penicillin and streptomycin, generated and determined the content of the first set of amendments to the FDCA. That is, the commercial success of products made the public and legislators aware of their existence showed legislators that these products would have a lasting impact on the public health.

Before the 1940s, legislators regulated drug products to prevent them from endangering the public health. The success of penicillin and streptomycin compelled legislators to recognize that drug products could truly improve the public health and that they could implement regulations to promote this process. They came to believe that the FDA ought to regulate the use and manufacture of drug products.

Correspondingly, legislators increased the scope of federal drug regulations in the 1940s to regulate these aspects of drug production. By the beginning of the 1950s, the federal government had complete authority over the use of prescription-only drugs and over the labeling, manufacture, and sale of drug products. Developments in the American drug market ultimately determined how Congress amended the FDCA.

Without the expedited development of penicillin during WWII, Congress would not have begun authorizing the creation of certification programs for antibiotic drug products. Similarly, without the success of penicillin and streptomycin as effective disease cures, Congress might not have perceived the need for requiring physicians' prescriptions for the sale of certain drug products.

Establishing Legal and Regulatory Precedents to for Regulating the Sale and Manufacture of Drug Products

The FDA's Bureau of Medicine handled the enforcement of the drug provisions of the FDCA. Within this Bureau, the Division of New Drugs managed and evaluated the submission of New Drug Applications. Although historians cite the 1938 Act as noteworthy for marking the inception of the premarket drug approval system, the New Drug Division employed few workers compared to other sections of the Bureau of Medicine. The New Drug Section of the FDCA affected the work of the FDA much less than did the Act's updated clauses prohibiting misbranded and adulterated drugs. FDA investigators and lawyers focused predominantly on prosecuting cases of misbranding during the early 1940s.⁸³ This section details the initial enforcement of the FDCA by the FDA and federal prosecutors as they attempted to remove dangerous products from the market. Furthermore, this section explains how Congress came to amend the FDCA for the first time in 1941, instituting a program to ensure the purity and quality of all insulin containing products.

⁸³ Goodrich, 20-25.

Prosecuting Firms For Selling Ineffective and Unsafe Drugs

Immediately following the enactment of the FDCA, the FDA worked to remove products from the market made illegal by the new law, including those that were dangerous or made false therapeutic claims. In 1940 the FDA began seizing misbranded products and prosecuting their makers to actively signal their intentions to drug makers.⁸⁴ The Elixir Sulfanilamide deaths convinced FDA administrators that the FDA should attend to the products of the drug industry actively. The FDCA changed the technical language of the regulations and generated changes in the FDA's methods of enforcement. Throughout the 1920s and 1930s, federal Food and Drug lawyers struggled to prosecute cases against firms selling products labeled with false therapeutic claims because the law required the state to prove a firm's intent to defraud in such cases. The 1938 Act removed this clause, allowing the state to prosecute a firm for labeling a product with false therapeutic claims without needing to prove intentional fraud. The Act defined a drug as "misbranded" when it was hazardous to health when used in the manner instructed on its label. This important clause would have allowed FDA inspectors to seize Elixir Sulfanilamide shipments on grounds that the product was dangerous rather than by claiming that the product was misbranded as an "elixir" because it did not contain alcohol.

Prior to 1938 the FDA employed fewer than ten lawyers who worked almost exclusively on preparing cases and corresponding with food and drug manufacturers. The FDA hired additional lawyers to handle the creation and adoption of new procedures requiring by the FDCA, including the approval of new drug products and

⁸⁴ Frederic Lee, "The Enforcement Provisions of the Food, Drug and Cosmetic Act," *Law and Contemporary Problems* 6, no. 1 (1939): 70-75.

the inspection of drug products for safety. William Goodrich, a lawyer for the USDA Solicitor Office's Food and Drug Division in 1939, claimed that the FDCA shifted the duties of federal lawyers towards more administrative work than in the past.⁸⁵ These lawyers also helped to set legal precedents for the new regulations, most notably in cases involving dangerous and ineffective drug products.

On a day-to-day basis, FDA employees worked to investigate the sale of misbranded and adulterated products. In 1940, the government transferred the FDA from the USDA to the Federal Security Agency (FSA), where it would remain until 1953, when the government would transfer it to the Department of Health, Education, and Welfare (HEW).⁸⁶ From its inception, the FDA was organized into four districts across the country, based in New York City, San Francisco, Atlanta, and Chicago. A District Chief managed the field inspectors and scientists who dealt with the products sold within that geographical area. Until an administrative reorganization in 1948, field inspectors and scientists reported directly to the District Chief and almost never dealt with the Washington Office.⁸⁷ The FDCA prohibited foods and drugs manufactured in unsanitary and inadequate factories; field inspectors spent a considerable amount of time in the early 1940s inspecting factories. Field inspectors collected samples from manufacturers by asking for voluntary samples, purchasing retail samples, compelling samples through legal proceedings, and through mandatory embargoes on international products. Chemists, biologists, and pharmacologists

⁸⁵ Goodrich, 1-10.

⁸⁶ In 1968 the FDA became a part of the Public Health Service within HEW and in 1980 the state remained HEW to the Department of Health and Human Services (HHS). The FDA is currently an agency within HHS.

⁸⁷ Winton Rankin, oral history by James Harvey Young, The FDA Oral History Series, September 30, 1980, The FDA History Office, Rockville, MD, 72-74.

within each district office analyzed these samples and advised the Chief as to the grounds for prosecution. Only the Chief could recommend that cases be sent to the FDA Commissioner in Washington, who then decided which cases to send to the U.S. Attorney's Office for prosecution.

While divisional inspectors focused on ensuring production standards within manufacturing sites, federal attorneys aimed to ensure the safety of properly manufactured drugs. In 1942 FDA inspectors dealt with a case involving a sulfathiazole product sold by the Winthrop Chemical Company, which had become contaminated with lethal amounts of phenobarbital, a drug used to treat seizures.⁸⁸ The Washington Office of the FDA learned of the contamination of this sulfa drug through the District Office in New York City. The Commissioner requested that the company recall the product completely. The Commissioner also requested that the company inform all potentially involved individuals of the drug's danger, including physicians, patients, retailers, and pharmacists. After the company had completed the recall, with the assistance of FDA administrators, the Commissioner instigated policies of stricter manufacturing inspections and required more manufacturing information on NDAs.⁸⁹

By 1950, federal courts had decided on several cases prosecuting drug manufacturers and drug retailers for violating laws prohibiting the sale of unsafe and ineffective drug products. Their decisions set precedents for future court decisions

⁸⁸ John Swann, "The 1941 Sulfathiazole Disaster and the Birth of Good Manufacturing Practices," *PDA Journal of Pharmaceutical Science and Technology* 53 no. 3 (1999): 148-152.

⁸⁹ Swann, "The 1941 Sulfathiazole Disaster," 152. This policy change was the beginning of the FDA's establishment of "good manufacturing practices," which they continue to update and enforce today.

concerning the sale and manufacture of drugs. In the 1943 decision of *United States v. Dotterweich*, justices determined that high-level administrators at drug firms could be prosecuted for a company's violations of the FDCA.⁹⁰ In the 1948 decision of *United States v. Sullivan*, Justice Black specified that the "purpose of the [FDCA] is to safeguard the consumer by applying its requirements to articles from the moment of their introduction into interstate commerce all the way to the moment of their delivery to the ultimate consumer."⁹¹ The FDA could therefore prosecute both drug manufacturers and drug retailers for the interstate sale of adulterated or misbranded drugs. A U.S. Court of Appeals in 1950 defined the term "adequate directions for use," as the need for firms to specify the disease conditions for which a drug is intended, as well as the dosage and frequency of administration of the drug.⁹² These cases defined the enforcement of the FDCA more thoroughly for both inspectors and federal prosecutors.

Marmola: The FDA's Case Against an Unsafe and Ineffective Drug Product

In the 1940s the FDA began to transition from acting as a strict policing agency to an educative body that taught firms how to comply with the new regulations. The FDCA limited multiple seizures of the same product, which forced the FDA to move away from its policy of seizing any and all possible misbranded or adulterated products, an approach that had dominated the agency during the 1920s

⁹⁰ *United States v. Dotterweich*, 320 U.S. 277 (1943) accessed February 3, 2012, <http://supreme.justia.com/cases/federal/us/320/277/>.

⁹¹ *United States v. Sullivan*, 332 U.S. 689 (1948), accessed February 3, 2012, <http://supreme.justia.com/cases/federal/us/332/689/case.html>.

⁹² *Alberty Food Products et al. v. United States*, 185 F.2d 321 (1950), U.S. Court of Appeals Ninth Circuit, accessed February 3, 2012, http://scholar.google.com/scholar_case?case=15447866825862266381&hl=en&as_sdt=2&as_vis=1&oi=scholar.

and 1930s.⁹³ The FDCA introduced a new possible procedure for dealing with manufacturers whose products violated the Act, especially those whose violations were uncertain. The state could now file an injunction, an official warning, notifying manufacturers about the faults of specific products, instead of completing potentially disruptive and lengthy seizures of such products. During the first several years after 1938, this procedure allowed the FDA to guide firms towards legal labeling while limiting animosity between themselves and private manufacturers.

In 1940 federal attorneys prosecuted the first case using the new regulations against the Raladam Company. The case concerned a weight-loss product that the company had produced since the early 1900s called Marmola.⁹⁴ FDA inspectors and scientists believed that Marmola was dangerous to health and attempted repeatedly to remove the drug from the market in the 1920s and 1930s. The FDCA did not compel firms to submit NDAs for existing drug products, so the FDA prosecuted firms for selling products they believed were unsafe after 1938. The FDA did not trust all firms to use the scientific principles that they endorsed to develop safe drug products.

The Marmola case reflects the impact of the expanded provisions of the FDCA that allowed the state to prosecute firms for selling drugs on the market the FDA believed were directly or indirectly hazardous to health. The FDA believed that Marmola's label recommended an unsafe dosage and falsely represented the product as a safe obesity cure "used by doctors the world over."⁹⁵ Although the product,

⁹³ Rankin, 13-20; Smith, Checchi, Goldhammer, 42-45.

⁹⁴ "Call for 30 Federal Witnesses for Drug Law Test," *Chicago Daily Tribune*, October 9, 1941.

⁹⁵ Federal Security Agency, Food and Drug Administration, "1251. Misbranding of Marmola Tablets" Notices of Judgment Under the Federal Food, Drug and Cosmetic

composed mostly of a thyroid extract, could induce weight loss, FDA scientists did not believe that it reliably cured obesity. The FDA argued that Raladam made a false therapeutic claim because a thyroid extract can only cure hypothyroidism, which does not cause obesity exclusively or consistently. However, the FDA principally charged the company with selling an unsafe product because it could cause hyperthyroidism, which causes a range of harmful, although not lethal, effects. Numerous medical professionals and chemists testified at the Marmola hearings. In 1945 the court found the firm at fault for selling a misbranded product. The court ordered the Raladam Company to destroy all of the Marmola products that had been seized by the FDA.

The Marmola case represents one of the first instances of the FDA prosecuting a firm for selling drugs labeled with false therapeutic claims. It illustrates that the provisions of the FDCA allowed the government to prosecute drug products on the market of which the FDA did not approve. Throughout the decade, federal lawyers prosecuted and won numerous cases against products solely based on firms' use of false therapeutic claims. In one of these cases, federal prosecutors charged the company with misbranding for producing an arthritis cure that the FDA had deemed ineffective called Nue-Ovo. Following testimony from medical and pharmacological experts, prosecutors claimed that the firm "represented and suggested that the article [Nue-Ovo] was a competent treatment for arthritis, whereas it was not."⁹⁶ The courts

Act, 1251-1300, (1945): 369-380, accessed January 18, 2012,

<http://archive.nlm.nih.gov/fdanj/bitstream/123456789/10142/14/ddnj01251.pdf>.

⁹⁶ Federal Security Agency, Food and Drug Administration, "1380. Misbranding of Nue-Ovo," Notices of Judgment Under the Federal Food, Drug and Cosmetic Act, 1351-1400, (1946): 457-460, accessed January 18, 2012,

<http://archive.nlm.nih.gov/fdanj/bitstream/123456789/10271/6/ddnj01380.pdf>.

upheld this belief and ordered the seized product to be destroyed in April of 1946; however, the courts could not prevent the firm from producing Nue-Ovo in the future. FDA employees continued to seize batches of products like Nue-Ovo even after courts had deemed them mislabeled. Often firms discontinued these products because of media coverage of the product's seizure and the financial strain of dealing with repeated seizures and trials. While the FDCA had faults, FDA employees used the law's provisions to remove numerous unsafe and ineffective drug products from the market.

Understanding Drug Safety in the 1940s

In the decade following the enactment of the FDCA, FDA administrators focused on enforcing the new standards of drug safety and accurate labeling of drug products. In requiring firms to prove that new drug products are "safe for use", the FDA raised the question of what "safe" meant; however, the legal concept of safety remained ambiguous throughout the 1940s. In the most straightforward manner, safe drug products are those that are not lethal to humans; however, most drug products cause nonlethal, but potentially painful and difficult side effects. Neither the FDA nor Congress established or codified a specific definition of drug safety in the 1940s. This meant that firms provided NDAs with all of the clinical and experimental data that they had accrued in relation to the product's safety, and medical officers used their personal judgment in deciding on the product's safety. The Marmola case illustrates that the FDA's concept of safety extended past lethality. FDA inspectors believed Marmola to be unsafe because it could cause hypothyroidism, a condition that causes disagreeable, but not intolerable, side effects like fatigue, joint pain, and dry skin.

In the 1940s, medical officers and other FDA officials began to consider the implications of the efficacy of a drug product in considering its safety. As shown by the FDA's prosecution of firms for selling drug products labeled with therapeutic claims that they believed were false, the FDA believed that drug products should be both safe and effective in the late 1930s and 1940s. In December 1944, the FDA published a report in conjunction with the AMA Council on Pharmacy and Chemistry that specified safety and efficacy as the main criteria used by conventional medical professionals and FDA medical officers in judging the merits of drug products.⁹⁷ This report, known as the Van Winkle report, claimed that one could not separate the concept of drug efficacy from the concept of drug safety. Medical officers in the FDA New Drug Division believed the extent to which one could tolerate a drug's dangerous or difficult side effects depended on its therapeutic value. FDA administrators also claimed that researchers must know the effective dosage of a drug in order to determine its safety.⁹⁸ To use a contemporary example, physicians use cancer treatments that cause immensely dangerous and unhealthy side effects; patients tolerate these side effects because of the drug's therapeutic benefit. A mild pain reliever would not be considered safe if it caused similar side effects.

The lack of a definition of drug safety caused inconsistencies in the content of NDA submissions and in the types of new products approved by the FDA. The FDCA did not require firms submitting NDAs to prove the efficacy of drug products; however, the FDA considered efficacy to some extent when reviewing applications.⁹⁹

⁹⁷ Carpenter, *Reputation and Power*, 115-116.

⁹⁸ Swann, "Sure Cure," 230-240.

⁹⁹ Carpenter, *Reputation and Power*, 119-125.

Firms needed to submit “full reports of investigations” proving the safety of drug products in NDAs, but many of them also included reports on drug efficacy.

Especially in the early 1940s, firms did not typically include exhaustive medical records from clinical trials, but they did include reports from physicians who used the drug for investigational purposes and lists of published studies on the drug’s use.¹⁰⁰

These documents often contained declarations of a drug’s efficacy. While the FDA had not fully standardized the NDA form, the 1938 Act pushed firms to include medical evidence supporting the therapeutic merit of their products in NDAs. While medical officers reviewing these applications considered efficacy and firms usually included some efficacy information in NDAs, FDA officials accepted ineffective new drugs during the 1940s and 1950s.

Considering the Impact of the Consistency of Certain Drug Products on the Public Health

The first major amendment to the FDCA, the Insulin Act, required both proof of efficacy and safety for the sale of all batches of insulin products. This amendment was the first case of a legal connection between safety and efficacy. By 1940, insulin had been used successfully as a diabetes treatment for over twenty years. Medical professionals believed strongly in the product’s merit and countless diabetes patients relied on insulin to live. Legislators passed the Insulin Act at the close of 1941 in response to the upcoming expiration of the University of Toronto’s patent on

¹⁰⁰ Smith, Checchi, Goldhammer, 1-10. This information was confirmed by the content of numerous NDAs from 1960-1963 in the FOK Papers at the Library of Congress.

insulin.¹⁰¹ After the patent's expiration, any manufacturer would have been able to label a product as insulin and the FDA would have had a great deal of trouble prosecuting all individual cases of adulteration and misbranding.

Prior to 1941, the University of Toronto had organized a private certification system for the manufacture of all insulin products. An internal board generated strength and purity standards and allowed several American firms to manufacture and sell insulin on the condition that the products conform to their standards. These firms, including Merck, Sharpe, and Dohme and Eli Lilly, had been producing insulin for diabetics through this system for several years before the University's patent was set to expire. Medical and health professionals presumably believed that loss of this certification process would allow manufacturers to flood the market with unstandardized insulin products. The medical community initiated a bill that would require the federal government to organize a similar system. Congress passed the bill quickly, because it had virtually no opponents and because the expiration of the University's patent was imminent.

In passing the Insulin Act legislators aimed to prevent firms from selling substandard insulin products and from falsely labeling products as insulin. The Act charged the FDA with creating a system of certification for all insulin products, essentially compelling the agency to take on the role previously held by the University of Toronto. This amendment offers another example of Congress modeling public regulatory systems after private ones. In 1941 the state adopted the

¹⁰¹Goodrich, 14-15. I sourced much of the information about the content and passage of the Insulin Act from this oral history interview with William Goodrich, a lawyer for the USDA and later the FSA, and the text of the amendment.

University's system of ensuring the consistency of insulin, just as they had adopted the AMA's system of approving drugs that they endorsed for the purposes of ensuring the safety of drug products.

Legislators defined the certification process for insulin products as one that would ensure "characteristics of strength, quality and purity...as necessary to adequately insure safety and efficacy of use."¹⁰² The FDA organized a system in which investigators used chemical assays that could determine the exact composition of insulin products to ensure the consistency of all insulin products. The passage of the Insulin Act demonstrates that the potential dangers of the unregulated production of a single chemotherapeutic could directly prompt federal legislation. Lobbies for the patent medicine manufacturers successfully eliminated an efficacy requirement for all new drugs from the FDCA. However, the passage of this amendment suggests that legislators did not completely oppose requiring firms to produce effective drugs, since it required the FDA to ensure the efficacy of all insulin products.

The passage of the Insulin Act also set a regulatory precedent that required certification programs for the manufacture of certain products. Between 1945 and 1949 legislators passed three additional amendments to the FDCA mandating certification processes for penicillin, aureomycin/chloramphenicol, bacitracin, and tetracycline.¹⁰³ These additions, along with the original amendment, illustrate how the FDA attempted to standardize ethical drug products among pharmaceutical firms

¹⁰² *The Insulin Act*, Public Law 336, *U.S. Statutes at Large* 55 (1941): 850.

¹⁰³ *The Penicillin Act*, Public Law 139, *U.S. Statutes at Large* 59 (1945): 463-464; *The Streptomycin Act*, Public Law 16, *U.S. Statutes at Large* 61 (1947): 11-12; *The Antibiotic Certification Act*, Public Law 16, *U.S. Statutes at Large* 63 (1949): 409-410.

using scientific analyses. These amendments also prompted the establishment of the FDA's Antibiotics Division, which managed the certification programs.

The passage of the Insulin Act illustrates that the federal government perceived the value of regulating the manufacture of effective drug products to ensure public health. The availability and widespread use of insulin and antibiotics like penicillin compelled legislators and administrators at the FDA Bureau of Medicine to consider how to regulate effective drug products to the public's advantage. Congress recognized that they could regulate drug products to improve the public health, rather than simply prevent injuries to the public health. Legislators determined that laws regulating effective drug products should not only control their sale and labeling, but also their manufacture, to ensure their consistent efficacy. Such consistency, they believed, would assist medical practitioners and the public in using these drugs successfully. Legislators and FDA officials reacted specifically and quickly to the drugs on the market during the 1940s by changing legislation to reflect their ideas of how to best serve the public health.

The Impact of World War II on the American Drug Market

In the 1940s, pharmaceutical firms, federal laboratories, and academic institutions introduced forty-nine new anti-infective agents to the market, more than twice the number of products in any other drug category.¹⁰⁴ While these organizations

¹⁰⁴ Paul de Haen, "Compilation of New Drugs 1940 thru 1975," *Pharmacy Times* 42 no. 3 (1976): 40-42. It is important to note that anti-infective agents are therapeutic drugs that inhibit or reduces the growth of any organism or virus invading the human body while the term "antibiotic" refers specifically to a therapeutic that inhibits or reduces the growth of a bacteria infecting the body "Antibacterial" is a term used to

introduced seventeen sulfonamide derivatives, they also introduced thirty-two products containing new anti-infectives, including anti-tuberculars, antiparasitics, antibiotics, and antibacterials. Two of the most heavily used and lasting anti-infectives developed by researchers in the 1940s were penicillin and streptomycin. This section examines the development and initial sale of penicillin in order to understand why legislators regulated this drug specifically in the late 1940s. The next section will examine the development of streptomycin.

The researchers instrumental in the development of penicillin had strong connections to the American effort during WWII. Wartime research accelerated the development of penicillin as a drug product. While researchers would have developed penicillin into a drug product without the war, they would not have developed the methods the government discovered to manufacture penicillin on a massive scale. Researchers developed penicillin as a drug product in a scientific manner; they performed *in vitro* assays, chemical analyses, and clinical trials. This research exemplifies the manner in which the FDA and medical professionals believed drugs should be developed and produced. However, it also serves to illustrate how the FDA believed drugs should be developed in the mid-1940s. The next chapter will return to the idea of using clinical trials to develop drugs, which the government did not regulate until the early 1960s.

describe any compound that inhibits or reduces the growth of bacteria. Not all antibacterial compounds are antibiotic drugs because they may be toxic to humans.

Funding Research to Develop Penicillin: Federal Programs During WWII

President Franklin D. Roosevelt established several bureaucratic organizations to manage the American war effort.¹⁰⁵ In June of 1940 he established the National Defense Research Council (NDRC) to coordinate scientific research concerning the war, which America had not yet entered. American scientists undertook two main scientific endeavors during the war: the development of weapons and the development of medical knowledge, including the development of drugs, for overseas forces.¹⁰⁶ The government initiated medical efforts in September of 1940 with the creation of the NDRC's Health and Medical Committee. The Committee members focused on preparing America for war by developing better medical techniques and technologies for dealing with battlefield medical crises.¹⁰⁷ This included developing better anti-infectives and treatments for surgical shock and establishing nutritious diets for troops in extreme conditions. In June of 1941, Roosevelt established the Office of Scientific Research and Development (OSRD), a more powerful independent body to dedicated to organizing and funding scientific research. The engineer Vannevar Bush directed the office until it disbanded in 1947.¹⁰⁸ The Committee on Medical Research (CMR) within the OSRD, led by Dr. Alfred N.

¹⁰⁵ David Adams, "Wartime Bureaucracy and Penicillin Allocation; the Committee on Chemotherapeutic and Other Agents, 1942-1944," *Journal of the History of Medicine and Allied Sciences*, 44, no. 2, (1989): 196-217.

¹⁰⁶ "Memo for Dr. Jewett: Resume for War Activities, Division of Medical Sciences, National Research Council," January 25, 1945, NAS OSRD Collection, NAS History and Description Folder, Medical Sciences 1941-1945.

¹⁰⁷ "Order Establishing the Health and Medical Committee," Council of National Defense Press Release, September 19, 1940, NAS OSRD Collection, NAS Council of National Defense Folder.

¹⁰⁸ Library of Congress, Science Reference Services, "The Office of Scientific Research and Development Collection," accessed January 19, 2012, <http://www.loc.gov/rr/scitech/trs/trsosrd.html>.

Richards, organized, performed, and assessed all medical research relevant to the war effort.

The CMR become highly instrumental in the development of penicillin as a widely used and effective drug product. In 1940, Richards recognized the potential benefits of a new chemical compound called penicillin, which several British scientists had begun researching for its anti-infective properties in the late 1930s.¹⁰⁹ Dr. Alexander Fleming discovered and isolated penicillin in the early 1930s in England. Chemists Howard Florey, Ernst Chain, and Norman Heatley continued his research in England and hoped to use the compound as a therapeutic agent to eradicate bacterial infections.¹¹⁰ When Great Britain entered the war in late 1939, these researchers lost their funding and went to America to continue their research. Richards encouraged penicillin research in America by funding private research on penicillin and by establishing federal programs to increase the scale and scope of penicillin investigation by public research facilities. Bush established a committee within the CMR to research useful chemotherapeutics for the American forces; researchers quickly found penicillin to be the most promising anti-infective.

The CMR's Committee on Chemotherapeutic and Other Agents (CCOA), headed by Dr. Chester Keefer, helped fund research on efficient penicillin production and organized clinical testing of its safety and efficacy. Keefer and his staff examined the results of all of the clinical trials investigators performed in the early 1940s to assess exactly which infections penicillin effectively cured. Keefer established

¹⁰⁹George Darling, "National Research Council: The Division of Medical Sciences in WWII Report", NAS OSRD Collection, NAS Council of National Defense Folder.

¹¹⁰Eric Lax, *The Mold in Dr. Florey's Coat* (New York: Henry Holt and Company, 2004), 6.

techniques for collecting clinical trial data, which commercial, governmental, and academic drug developers adopted during and after the war. This is not to say that researchers had not previously used clinical trials in developing and analyzing the merit of drugs. Rather, Keefer refined techniques for organizing trials around the country and gathering this large quantity of clinical data into a cohesive whole with definite conclusions.

Richards convinced investigators at the USDA's Northern Regional Research Alliance Laboratories (NRRL) in Illinois to take on penicillin research and to employ Florey, Chain, and Heatley. The laboratories at NRRL discovered that penicillin could kill numerous bacterial strains by using a technique known as cross-streaking. Researchers would deposit a specific amount of the penicillin compound onto an isolated bacteria colony and would then evaluate the impact of the chemical on the bacteria's growth over time. In using this technique researchers found numerous strains of bacteria that penicillin could kill. Researchers, however, struggled to discover an efficient method of growing penicillin in the amounts necessary to perform comprehensive clinical trials. To obtain penicillin, one must isolate the compound from a specific species of mold; massive amounts of this mold are required to accumulate enough penicillin to treat human infections. In the early 1940s researchers at both private and public organizations focused on two types of penicillin research: medical researchers examined the therapeutic effects of penicillin, while chemists worked to establish more effective methods of penicillin production.

Researchers across the country were interested in using penicillin to treat their patients because of the extensive positive publicity the drug had received in the early

1940s.¹¹¹ At this time, medical professionals had used sulfa drugs for several years to treat various infections, including blood infections and staphylococcal infections. However, researchers had also documented infections and strains of bacteria resistant to the antibacterial effects of those drugs. The sulfa drugs are antibacterial agents, meaning that they reduce bacterial infections, rather than eliminate them. Researchers believed penicillin could be a true antibiotic that could cure number of diseases, including those the sulfa drugs could not treat. This possibility interested numerous physicians across America. However, since American researchers began penicillin research during the war, the government took control over penicillin supplies in America. Keefer described the status of penicillin research in November of 1942:

Several pharmaceutical companies have been making small amounts of penicillin for experimental purposes under an agreement with the Committee on Medical Research. The Committee on Chemotherapeutic and Other Agents has been requested to supervise its experimental testing. A very small amount of material has been available and all of it has been used for the study of a few infections, which are of importance to the armed forces. The present production has not been able to meet the needs and demands for experimental study, let alone its general distribution.¹¹²

Although Keefer denied having complete control over American penicillin stores, the public, many medical researchers, and physicians saw the CCOA as the gatekeeper of the American penicillin supply. Until May of 1944, Keefer's Office of Civilian Penicillin Distribution allocated the national penicillin supply; civilians could not

¹¹¹ "Nine Concerns to Make Wonder Drug Penicillin," *Los Angeles Times*, August 30, 1943; "Penicillin," *The New York Times*, September 3, 1943; "Potent Penicillin, Drug May Save Life of Girl, 2, a Victim of Septicemia Here," *The New York Times*, August 13, 1943.

¹¹² Letter from Chester Keefer to The Los Angeles Breakfast Club, November 20, 1942, NAS OSRD Collection, Committee On Chemotherapeutic and Other Agents Folder.

purchase the drug and the state limited its use to patients with diseases of interest to the military.¹¹³ These included streptococcal and staphylococcal infections resistant to the sulfonamides, pneumococcal meningitis, and syphilis. Keefer and his staff analyzed the results of all of the cases in which penicillin had been used on humans. They informed the military of the diseases penicillin had treated successfully and the observed side effects and non-toxic dosages of the drug. Keefer developed specific protocols for using penicillin as a treatment for specific bacterial infections.¹¹⁴

The CCOA expedited the process of developing penicillin as a marketable drug product by encouraging many private and public institutions to perform research on the drug and by compiling the data obtained by all of these institutions. The government maintained the importance of the search for efficient penicillin production and declared that the state would purchase all possible supplies of penicillin.¹¹⁵ Researchers at the NRRL, including Florey, focused on identifying a more effective method of producing penicillin. In addition to this publicly funded institution, many private firms invested considerable time and money in penicillin research. Beginning in 1942 the government entered into several contracts with commercial and academic pharmaceutical research firms agreeing to exchange all

¹¹³ Memo from Committee on Chemotherapeutic and Other Agents to the NRC, September 23, 1943, NAS OSRD Collection, Committee On Chemotherapeutic and Other Agents Folder.

¹¹⁴ Meeting Minutes, Committee On Chemotherapeutic and Other Agents, December 28, 1943, NAS OSRD Collection, Committee On Chemotherapeutic and Other Agents Folder.

¹¹⁵ Statement by the Food and Nutrition Board, March 1944, NAS OSRD Collection, Committee On Chemotherapeutic and Other Agents Folder.

information on penicillin production.¹¹⁶ In 1944 the government created the official Penicillin Synthesis Program, which fostered the exchange of information between all of the laboratories with which the government held contracts. The government aimed to prevent firms from duplicating similar studies and to establish a royalty-free license for penicillin sold to the military.¹¹⁷ Although researchers did not discover a synthetic form of penicillin until 1958, NRRL increased its monthly penicillin production rates from one hundred million units in September of 1941 to almost nineteen billion units in late 1944.¹¹⁸

During WWII, private and public research institutions influenced each other and cooperated to development of new drug products, new forms of drug manufacture, and new forms of drug development. Private drug firms collaborated with temporary government bodies created increase the efficiency of scientific research. These bodies used highly scientific and exact investigation techniques, including clinical trials. In addition to penicillin, the government performed and funded research on a number of other chemotherapeutic agents during the war. The government explored the possible use of amphetamines as effective stimulants for the

¹¹⁶ The government did not fund any research performed by private firms, but it did provide some funding for academic institutions. This standard displays the already present belief that research for commercial firms was more lucrative than academic research.

¹¹⁷ "The Penicillin Synthesis Program" July 31, 1944, NAS OSRD Collection, Penicillin Synthesis Program Folder.

¹¹⁸ Paul de Haen "Historical Drug Mini-Review" 1954-1982" *New Drug Parade*, September 30, 1983; Peter Neushul, "Science, Government, and the Mass Production of Penicillin," *Journal of the History of Medicine and Allied Sciences* 48, no. 4, (1993): 391-394.

armed forces, notably a product from Smith, Kline and French called Benzedrine.¹¹⁹ Researchers employed and funded by OSRD hoped to determine that Benzedrine could assist stressed and sleep-deprived soldiers and pilots. War efforts did not directly affect Benzedrine's development or production since it had already been marketed as an antidepressant for a decade. Although government researchers did not determine conclusively that amphetamines were more effective stimulants than caffeine, the military provided soldiers with the drug beginning in early 1943. Historian Nicolas Rasmussen claims that directors at Smith, Kline and French convinced OSRD administrators to use the product partly because the British government was already using the drug for its forces.¹²⁰ Meetings between Smith, Kline and French and the OSRD illustrate the influence of private commercial firms on the government's decision-making processes.

Expediting the Development of Drug Products and Methods of Manufacture

Penicillin was the first effective cure for infectious diseases. In response to the emergence of a truly effective drug, the legislators concluded that the FDA should be able to regulate its manufacture to ensure its consistent efficacy. After the war, penicillin products became immensely successful all over the country as physicians prescribed the drug for virtually all patients with pneumonia, syphilis, and many other infectious diseases. By 1949, twenty American drug companies were selling

¹¹⁹ Nicolas Rasmussen, "Medical Science and the Military: The Allies' Use of Amphetamine during World War II," *Journal of Interdisciplinary History* 42 no. 2 (2011): 220-227.

¹²⁰ Rasmussen, "Medical Science," 215-223.

penicillin products.¹²¹ The nationwide usage of penicillin, a drug more effective than any other anti-infective previously available, caused the FDA to reconsider the effectiveness of the FDCA in regulating drug products to both improve and ensure the public health. Penicillin's prominence caused Congress to pass an amendment to the FDCA in July of 1945 requiring the FDA to create a certification program for penicillin products sold to the public, just as it had done for insulin products. When issues with the manufacturing of sulfathiazole, a moderately effective antibacterial agent, surfaced in 1942, the FDA increased its inspections of manufacturing facilities, but did not call for amending the FDCA to allow for the certification of all sulfathiazole products. Issues with the safety of other, less prominent drug products, like sulfathiazole, did not cause concern equal to that evoked by the prospect of ineffective penicillin or insulin.

I argue that the government's role in penicillin production likely increased Congress' awareness of the drug and facilitated the passage of the Penicillin Act in 1945. By the end of WWII, researchers and medical professionals agreed upon penicillin's safety and effectiveness in treating several infectious diseases. Much like the insulin case, legislators rightly presumed that medical professionals would support standardizing penicillin products and a program to ensure its safety and efficacy. World War II organizational bodies accelerated the development of penicillin as a drug product. The OSRD coordinated research that changed how medical researchers performed clinical trials and how firms produced drugs on a large scale. Changes in firms' abilities to manufacture drugs on a large scale allowed them

¹²¹ Council on Pharmacy and Chemistry, American Medical Association, *New and Nonofficial Remedies*, (Philadelphia: J. B. Lippencott Company, 1949): 148-159.

to produce and sell more products, increasing the percent of the population receiving penicillin. After the war, controlled clinical trials began to surpass the testimonials of physicians as the standard of proof for drug safety and efficacy. The OSRD's involvement in penicillin research yielded a product that changed legislators' approach to regulation. Doctors could and did prescribe penicillin to virtually anyone in America, while they could only prescribe insulin to diabetics, a very specific subset of the population. By establishing a system to determine the "strength, quality, and purity" of penicillin products to "insure safety and efficacy in use", Congress signified that they supported such standards for any drug, regardless of its patent status or specific use. Furthermore, the Penicillin Act precipitated the establishment of certification programs for most other scientifically developed antibiotics, including streptomycin.

The FDCA regulated the sale and development of drug products by directly requiring firms to establish their safety. Legislators used the Insulin and Penicillin Acts to regulate drug manufacture, a previously unregulated aspect of the drug production process. After World War II, ethical drug firms emerged as members of a unified pharmaceutical industry. These companies, including Eli Lilly, Merck, Sharpe and Dohme, Pfizer, Bristol-Myers, Upjohn, Parke-Davis, and Squibb, developed drug products using scientific principles of the time. These included the use of chemical chromatography, protein purification, and enzyme analysis to determine the lasting effect of compounds on the human body. They employed scientists to develop drug products, performed clinical trials, and produced increasingly effective drug products in the 1940s. While imperfections in these methods meant that these companies also

produced various ineffective and unsafe drug products, they instituted policies of using rational scientific principles to avoid this.

The FDA, Antibiotics, and Physician's Prescriptions

During the war, the government advanced and funded research that increased the capabilities of the pharmaceutical industry to produce effective drugs in large quantities. In the latter half of the decade, these drugs prompted further amendments to the FDCA concerning the use of drugs prescribed by physicians, another unregulated aspect of the drug production process. I argue that the continued prevalence of penicillin and streptomycin compelled legislators to regulate physicians' prescriptions of drugs products. This section details the emergence of streptomycin, another effective antibiotic, and argues that this product was important in proving that penicillin was not an anomaly. Streptomycin convinced Congressmen that effective drug products could become the norm. This section also details evolution of the FDA, as a bureaucratic agency, and its changing relationship with the pharmaceutical industry during the 1940s. By the end of the decade, their relationship had become more collaborative, which facilitated the introduction of regulations that gave the FDA the authority to decide what drug products could be sold only with a physicians' prescription.

Accepting and Promoting of the Practices of Employees of the Pharmaceutical Industry: The FDA in the Late 1940s

As an agency, the FDA retained its staff over time, which likely impeded change within the agency, as argued by former employees.¹²² As mentioned previously, the FDA slowly began the process of transitioning into an educative, monitoring body in the 1940s. Political scientist Daniel Carpenter has asserted that the mentality of the FDA in the 1920s and 1930s was one of “regulation by inspection and enforcement,” where the FDA prosecuted cases of drug fraud and adulteration vigorously.¹²³ During this time, FDA administrators focused on eliminating illegal products from the market, rather than preventing illegal products from entering the market. By the early 1920s, all of the men who would become FDA Commissioners in the 1940s and 1950s had started their careers working at the FDA. These included Walter Campbell, FDA Commissioner from 1937 until 1944, Paul Dunbar (1944 – 1951), Charles Crawford (1951 – 1954), and George Larrick (1954 – 1965).

While drug firms grew as companies during WWII, the FDA’s regulation of foods and drugs stagnated during the war because numerous FDA employees enlisted overseas. The remaining staff dealt mostly with existing issues and legal proceedings and did not actively investigate many new cases. This included the prosecution of firms that had sold dangerous and ineffective drug products before 1938, detailed earlier in this chapter. The agency did not begin to accept and adapt to the changing drug industry until the second half of the 1940s, when Dunbar became Commissioner. Under Dunbar, the FDA gradually moved away from the policing tactics of the old

¹²² Rankin, 51-60, 117-119.

¹²³ Carpenter, *Reputation and Power*, 125.

agency because of the changing drug market. Dunbar, a chemist by training, emphasized the need for understanding and utilizing contemporary science in performing the FDA's duty to protect public health. Both FDA inspectors and lawyers respected Dunbar for his attempts to pass necessary food and drug legislation and to establish protocols ensuring the sale of safe products.¹²⁴ Dunbar believed in the need for extensive chemical analyses of food and drugs products to ensure their safety and in the regulation of addictive and dangerous drug products. This correlated with the new practices of employees of the pharmaceutical industry.

In the 1940s conventional medical professionals became completely dependent on established science. Medical researchers developed drug products using new discoveries in medical knowledge and new tools of scientific experimentation. Chemists developed techniques and tools of chromatography, a process by which one separates mixtures into specific compounds. This allowed researchers to isolate and analyze the therapeutic value of specific compounds more precisely than in the past. Molecular biologists developed new methods of purifying and isolating human proteins. Initially researchers used these techniques to examine specific blood proteins to create artificial plasma. Researchers employed by the pharmaceutical industry also used these purification techniques to assess the impact of chemicals on specific human proteins to develop drug products. They continued to experiment with the possible therapeutic merit of known chemical compounds as well. Some

¹²⁴ Smith, Checchi, Goldhammer, 164; Goodrich, 65-70.

companies developed drug products containing chemicals traditionally labeled as toxic to treat cancer.¹²⁵

In the years immediately following WWII, the emergence of the scientifically based pharmaceutical industry impacted the FDA's internal policies and broad objectives. Two trends support this claim. First, FDA administrators and inspectors began to move away from seizing materials and towards using injunctions and requesting recalls from companies producing unlawful drugs.¹²⁶ Second, FDA scientists focused increasingly on the issue of the long-term toxicity of both drug products and food additives and performed their own experiments on long-term toxicity.¹²⁷ Winton Rankin, an FDA administrator from the 1940s to the 1960s, recalled that in the early 1940s the FDA performed fewer than ten recalls a year, but that this number reached the fifties in the following decade.¹²⁸ Their use of recalls illustrates that the FDA cooperated with the drug firms in attempting to ensure the sale of safe and lawful drugs. One cannot attribute the increase in recalls to any single event, person or product. Rather, it can be seen as a reaction to the growing authority of medical science and the government's growing trust in the pharmaceutical industry to act to ensure the public health.

The FDA's focus on long-term toxicity studies demonstrates that they recognized that scientific advancements in production brought both new therapeutic

¹²⁵ "Milestone 1949: Mechlorethamine, ethinyl estradiol, TEM, mercaptopurine, methotrexate, busulfan," *Developmental Therapeutics Program*, National Cancer Institute, accessed February 2, 2012, http://dtp.nci.nih.gov/timeline/noflash/milestones/M2_1949.htm.

¹²⁶ Smith, Checchi, Goldhammer, 40-51; Goodrich, 72; Rankin, 24.

¹²⁷ Carpenter, *Reputation and Power*, 125-135.

¹²⁸ Rankin, 24-26.

possibilities and new complications and dangers. Medical officers at the Division of New Drugs appealed for long term toxicity studies from firms submitting NDAs. Scientists within the FDA also performed long term toxicity tests on drug products already on the market. In taking on the role of continuing the scientific investigations of pharmaceutical companies after a drug's market approval, the FDA signaled their trust in scientific methods of drug analysis and their misgivings about the exhaustive use of these methods by pharmaceutical firms. While the FDA came to trust pharmaceutical companies to recall unsafe drugs in the 1940s, they still worried about the potential health risks of sale of unsafe drugs. This concern arose from past experiences with the drug market (the Elixir Sulfanilamide and Marmola). The FDA also knew that physicians had begun prescribing certain drug products to the same patients repeatedly, especially penicillin and streptomycin. A physician could prescribe a typical patient with penicillin yearly throughout his life; this possibility motivated FDA officials to perform long-term toxicity testing on popular drug products.¹²⁹

The FDA's actions during the 1940s and 1950s demonstrate that the state accepted scientifically based medicine and drugs as the superior conventional standard. FDA medical officers required clinical and chemical analyses for new drugs entering the market and performed assays to determine the exact chemical composition of drugs. Federal lawyers used the testimony of conventional, scientifically trained physicians, and pharmacologists to prosecute drug firms that violated the law. By 1950, the FDA expressed their favor for NDAs that firms

¹²⁹ Carpenter, *Reputation and Power*, 129-130.

submitted with toxicological and pharmacological studies. The pharmaceutical industry of the late 1940s demonstrated the same emphasis on profit through mass marketing displayed by the patent medicine industry in previous decades. Companies continued to sell proprietary medicines and other unconventional therapeutics into the 1950s.¹³⁰

Defining Antibiotics and the Discovery of Streptomycin

In his comprehensive *Compilation of New Drugs*, Paul de Haen cites the introduction of 202 “single chemical entities or synthesized drugs not previously available in the United States” in the 1940s, including almost fifty anti-infective agents.¹³¹ During the 1950s firms introduced 421 new drugs to the market, including over eighty anti-infective agents. The success of penicillin as a commercial product demonstrated the potential profitability of therapeutically effective drug products to drug manufacturers. The developers of penicillin displayed the potential financial gains firms could obtain by producing antibiotic drug products. In the late 1940s firms began producing more drugs products and continued to produce large proportions of anti-infective drug products.

The AMA publication *New and Nonofficial Remedies* listed the therapeutics regarded as both safe and effective by the AMA’s Council on Pharmacy and Chemistry. This publication allows one to chart the drugs of which conventional physicians were aware and used in a given year. In 1942 and in 1949, the editors devoted an almost identical number of the publication’s pages to anti-infective agents,

¹³⁰ James Harvey Young, “The Persistence of Medical Quackery in America,” *American Scientist* 60, no. 3 (1972): 319.

¹³¹ de Haen, “Compilation of New Drugs 1940 thru 1975,” 40-42.

144 and 141 respectively, out of about 600 pages.¹³² In 1942 the Council mostly listed inorganic metal compounds, alcohols, and salts as anti-infective agents, with the only exception being the “antibacterial agents” known as the sulfonamide compounds.¹³³ By 1949, the Council had introduced a new category of anti-infective agents called “antibiotics,” which included only penicillin and streptomycin; they continued to label the sulfonamide compounds as “antibacterial agents”. They defined antibiotics as therapeutics with bacteriostatic or bactericidal properties, meaning they could inhibit bacteria reproduction or kill bacteria completely.¹³⁴ The term “antibacterial agents” described any therapeutic that could reduce the growth of bacteria. The pharmaceutical industry developed a range of new antibiotics, hormone drugs, and cardiovascular regulating agents available to conventional physicians and the public in the 1940s. Less than a year after physicians began using penicillin extensively in 1945, the Merck Company began selling streptomycin, another effective antibiotic.

The success of penicillin justified the FDA’s endorsement of the usage of biochemical assays and clinical trials in developing drug products, which were also used in developing streptomycin as a drug product. In 1943 microbiologists at Rutgers University discovered that streptomycin, a chemical secreted by specific

¹³² Council on Pharmacy and Chemistry, American Medical Association, *New and Nonofficial Remedies*, (Philadelphia: J. B. Lippencott Company, 1942): 76-220; Council on Pharmacy and Chemistry, American Medical Association, *New and Nonofficial Remedies*, (Philadelphia: J. B. Lippencott Company, 1949): 66-207.

¹³³ Unlike organic compounds, very few inorganic compounds originate from any living organism, such as a mold, bacteria or animal tissue. Many of therapeutics developed in the 1940s and 1950s using scientific techniques, especially antibiotics, were organic compounds, such as penicillin, streptomycin, and amphetamine.

¹³⁴ Council on Pharmacy and Chemistry, American Medical Association, *New and Nonofficial Remedies*, (Philadelphia: J. B. Lippencott Company, 1951): 109.

species of soil-dwelling bacteria, inhibited the growth of tuberculosis bacteria.¹³⁵

These researchers were members of the growing field of pharmacology. They aimed to discover potential therapeutics by screening microorganisms for the potential production of antibiotic compounds.¹³⁶ They isolated countless bacterial strains and the compounds they secreted in the hope that competing bacteria species would secrete compounds toxic to each other. They then employed the cross-streaking technique to assess the compounds' antibacterial activity. Researchers working on penicillin also employed this technique. After establishing the antibacterial action of streptomycin, researchers outsourced animal testing to the Mayo Clinic, a nonprofit medical research facility in Rochester, Minnesota. Investigators at the Mayo Clinic successfully established the safety of streptomycin in animals and then began clinical trials.¹³⁷ By the end of 1944, the Clinic had used streptomycin to cure multiple patients of tuberculosis and urinary tract infections. Researchers at the Mayo Clinic and Rutgers developed streptomycin on a much smaller scale than did those working on penicillin. The national research effort on penicillin expedited its development as a drug product, but the discovery of streptomycin illustrates that this massive effort was not necessary to develop effective and commercially successful drug products.

In 1945 the editors of *JAMA*, *Science*, and *The New England Journal of Medicine* published multiple studies analyzing the streptomycin's therapeutic value

¹³⁵ Milton Wainwright. "Streptomycin and Resultant Controversy," *History and Philosophy of the Life Sciences* 13 no. 1 (1991): 97-124.

¹³⁶ Wainwright, "Streptomycin and Resultant Controversy," 103.

¹³⁷ Wainwright, "Streptomycin and Resultant Controversy," 108. This process of first performing *in vitro* studies, and then determining safety with animal testing, and lastly determining both safety and efficacy of drug products using clinical trials was adopted by drug firms in the 1940s and 1950s; the federal government required this process in 1963.

and heralded it as the first tuberculosis cure.¹³⁸ It is likely that Rutgers, who had paid the Mayo Clinic to perform clinical trials on streptomycin, sold their information on the drug compound to Merck. Merck then developed a drug product using this antibiotic compound and applied for an NDA for “Streptomycin Sulfate Ampoules” in 1946.¹³⁹ The FDA’s New Drug Division approved the application that same year. Physicians continue to use streptomycin to treat tuberculosis and other infections today. Streptomycin and penicillin represent the first effective antibiotics introduced onto the American market. In 1947 legislators established a certification programs for all products containing streptomycin.¹⁴⁰ By 1949, seven pharmaceutical companies in America sold streptomycin products.¹⁴¹ Streptomycin’s medical success demonstrated to Congress that truly effective drug products could become the norm on the American drug market. The country learned that penicillin was not an anomaly.

Since they performed much of their research concurrently, the developers of penicillin did not directly influence the work of researchers at Rutgers and Merck developing streptomycin. However, researchers developed these drugs using similar scientific techniques and protocols endorsed by the FDA in the late 1940s. The FDA preferred firms to include animal testing and human clinical trials in New Drug

¹³⁸ “Streptomycin For Typhoid: A Pharmacologic Study,” *The Journal of the American Medical Association* 128 no 3 (1945): 175-180; Kuel F. et al., “Streptomyces Antibiotics. I. Crystalline Salts of Streptomycin and Streptothricin,” *Science* 102 (1945): 34-35; D. Anderson and M. Jewell, “The Absorption, Excretion and Toxicity of Streptomycin in Man,” *The New England Journal of Medicine* 233 (1945): 485-491.

¹³⁹ National Academy of Sciences, National Research Council, “NDA #60604 – Streptomycin Sulfate Ampoule, USP, Approved August, 14, 1946,” *Drug Efficacy Study*, obtained through FOIA request, submitted November 16, 2011.

¹⁴⁰ *The Streptomycin Act*, Public Law 16, *U.S. Statutes at Large* 61 (1947): 11-12.

¹⁴¹ Council on Pharmacy and Chemistry, American Medical Association, *New and Nonofficial Remedies*, (1949): 159-162.

Applications, but the New Drug Division did not refuse many NDAs. The Division approved over 4500 NDAs from the enactment of the FDCA through 1949, about two thirds of the NDAs they received during this time.¹⁴² While the FDA received thousands of NDAs for new drug products, many of these products contained the same molecular entities, or drug compounds. The FDA received dozens of NDAs for penicillin drug products varying in dosage and form (liquid, pill, nebulizer) from a number of pharmaceutical firms.

Mandating Physicians' Prescriptions for the Sale of Specific Drugs

Before Congress began to consider how to further regulate drug development, they dealt with regulating another aspect of drug production: the use of physicians' prescriptions.¹⁴³ Congress amended the FDCA to define the process of physicians' prescription of drug products for the same reasons that they amended the FDCA to regulate drug manufacture. In both cases, Congress and the FDA responded to the widespread use of effective antibiotics, penicillin and streptomycin, by enacting regulations to ensure the continued and consistent effectiveness of these products. I argue that Congress enacted these regulations based on the belief that consistency in drug products themselves and in how the public used them would increase the ability of these products to improve the public health.

¹⁴² John Swann, "Summary of NDA Approvals and Receipts, 1938 to the Present," *The Food and Drug Administration*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm>, accessed March 15, 2012.

¹⁴³ As of 1950, the Harrison Anti-Narcotics Act of 1914 was the only legislation that legally required a physician's prescription for the sale of therapeutic drugs. However, it concerned only the sale of narcotic substances.

The amendments to the FDCA proposed by the FDA in the late 1940s reflect their devotion to medical science and recently developed relationship with the pharmaceutical industry. In 1951 Commissioner Dunbar announced his retirement from the FDA. The Federal Security Agency declared Assistant Commissioner Charles Crawford his successor. In 1942 Crawford had proposed an amendment to the FDCA that would have defined prescription drug products as those products that could not be sold safely with adequate directions for use and prevented firms from labeling any other products as prescription drug products.¹⁴⁴ Although his idea was not put into law, FDA administrators wanted to control physicians' prescribing practices throughout the 1940s. In the late 1940s FDA officials took up the issue of prescriptions and fought to pass an amendment to the FDCA that would give the agency the authority to produce and maintain a list of drug compounds that could be only sold with a physician's prescription.¹⁴⁵ The FDA also hoped to specifically detail the process of refilling prescriptions.

Public health workers and FDA administrators began to doubt the effectiveness of the FDCA's provisions for prescription drug products because of the increased use of drug products introduced in the 1940s, mainly the new antibiotics streptomycin and penicillin. The FDCA, as enacted in 1939, provided that firms could choose to label drug products as prescription-only or, by default, as over-the-counter (OTC) products. The law exempted firms from the FDCA's labeling requirements for

¹⁴⁴ Goodrich, 16-17.

¹⁴⁵ Swann, "Sure Cure," 60; Goodrich, 16.

products labeled with “by prescription only.”¹⁴⁶ FDA administrators believed that the public’s use of penicillin and streptomycin products without medical supervision would decrease their effectiveness and allow drug firms to exploit the public’s naiveté.¹⁴⁷ Firms could sell any non-narcotic drug without requiring a physician’s prescription, and consequently without requiring physicians’ approval or acceptance. In addition, firms could use the “by prescription-only” label to avoid federal labeling requirements. FDA officials also worried about the refilling of physicians’ prescriptions for both narcotic and non-narcotic drugs; federal law did not address prescription refilling and FDA officials hoped to limit or eliminate pharmacists’ power to refill prescriptions because this could also result in unsupervised use of drug products.¹⁴⁸

In 1944 the FDA defined prescription drug products in the *Federal Register* as those whose,

Toxicity or other potentiality for harmful effect or the method of its use or the collateral measures necessary to its use, is not generally recognized among experts qualified by scientific training and experience to evaluate its safety and efficacy, as safe and efficacious for use except by or under the supervision of a physician, dentist, or veterinarian.¹⁴⁹

¹⁴⁶ *The Federal Food, Drug, and Cosmetic Act*. Public Law 717. *U.S. Statutes at Large* 52 (1938).

¹⁴⁷ John Swann, “FDA and the Practice of Pharmacy: Prescription Drug Regulation before the Durham-Humphrey Act of 1951,” *Pharmacy in History* 36 no. 2 (1994): 59-60.

¹⁴⁸ In addition to the allowance of prescription refilling, FDA and FSA officials were also concerned about the legality of telephoned prescriptions and telephoned

¹⁴⁹U.S. National Archives and Records Administration, *Federal Register* 9, no. 12255 (1944), cited in Gregory W. Reilly, “The FDA and Plan B: The Legislative History of the Durham-Humphrey Amendments and the Consideration of Social Harms in the Rx-OTC Switch,” written for The Harvard Law School (2006): <http://leda.law.harvard.edu/leda/data/787/Reilly06.html#fnB32>, accessed March 17, 2012.

This definition of prescription drug products relied upon the perceptions of “experts”; it was a suggestion to firms concerning the categorization of drug products. The power to sell drug products by prescription only or over-the-counter still rested with drug manufacturers. In the late 1940s FDA administrators sent directives to drug manufacturers urging them to sell products containing certain drugs, including penicillin and streptomycin, by prescription only.¹⁵⁰ Administrators believed that firms could not prevent the public from misusing their effective and complex drug products simply by labeling them with the required “adequate directions for use”. For this reason, the FDA informed firms that their medical officers believed that licensed physicians should be involved in the public’s use of some specific drug products. Federal prosecutors, legislators, and FDA officials had not legally defined the act or implication of physicians prescribing drug products or the pharmacist’s role in that process.

In April of 1949 and June of 1950, Representative Carl Durham, a pharmacist from North Carolina, sponsored bills proposing to amend the FDCA to detail the process of physicians’ prescription of drug products.¹⁵¹ Congress mainly ignored these bills due to public apathy on the subject and their preoccupation with President

¹⁵⁰ Swann, “Sure Cure,” 60.

¹⁵¹ The legislative history of this amendment was sourced from a paper written recently for a Harvard Law School class. The author, Gregory Reilly, sourced much of this paper from the 1979 article in the *Food and Drug Law Journal*, published by the FDA (FDA, “Legislative History of the Federal Food, Drug and Cosmetic Act and Its Amendments,” 1-2, (1979)).

Truman's attempts to pass his Fair Deal reforms.¹⁵² In March of 1951 Durham and Hubert Humphrey, also a pharmacist from North Carolina, introduced companion bills into Congress, H. R. 3298 and S. 1186, respectively.¹⁵³ These bills proposed to amend the FDCA by defining prescription-only drugs that could be exempt from the labeling provisions of the FDCA. Essentially, Durham and Humphrey aimed to include the FDA's 1944 definition of prescription drugs in the federal law. The original H. R. 3298 defined prescription drugs as those that could not be used safely or effectively without a physician's supervision, but the committees chose to eliminate the word "effectively" because of industry objections. The industry continually opposed laws mandating drug efficacy in the 1930s, 1940s, and 1950s simply because such laws would require more work in drug production.

As pharmacists, Durham and Humphrey wrote legislation that they believed would reduce legal action against pharmacists for selling drugs labeled "by prescription-only" without a physicians' prescription.¹⁵⁴ The Congressmen aimed to establish further external regulation of the pharmaceutical industry. The bills authorized the Federal Security Agency, of which the FDA was a part, to mandate that any drug product whose toxicity or dangerous effects made it unsafe for use without a professional diagnosis could be sold only with a physician's prescription.¹⁵⁵

¹⁵² Brinkley, *The Unfinished Nation*, 761-762. Truman's Fair Deal attempted to expand on President Roosevelt's new Deal reforms by increasing Social Security benefits and raising the minimum wage, but failed to do so.

¹⁵³ Reilly, "The FDA and Plan B".

¹⁵⁴ Robert Bud, "Antibiotics, Big Business, and Consumers: The Context of Government Investigations into the Postwar American Drug Industry," *Technology and Culture* 46 no. 2 (2005): 340-341.

¹⁵⁵ Peter Temin, *The Origin of Compulsory Drug Prescriptions*, (Cambridge, MA: MIT Press, 1978), 18.

The Congressmen argued that the FDA should be given this authority because the current system lacked standardization and permitted the sale of unsafe products. The bill called for the government to standardize which drug products could be sold only with a prescription.

Over the summer of 1951, Durham and other Congressmen amended this bill to require firms to sell certain non-narcotic drug products by prescription-only. That is to say, the FSA would not only define which drug products should be considered prescription drug products, but the law would also require firms to sell those products by prescription-only. The bill would require firms to sell all products containing habit-forming drugs, drugs used before the FDA accepted a firm's NDA (also known as investigational drugs), and drugs experts believed could not be safely used without a physician's oversight by prescription-only. The Senate and House committees reviewing these bills approved of this addition. Some Congressmen opposed the bill because it limited the patient's right to self-medication and because increased the power of the licensed physician.¹⁵⁶ Congressmen debated who should be empowered to decide which drug products fit the definition of prescription-only drugs.

Representative Joseph O'Hara suggested removing this authority from the FSA Administrator, which the bills then declared. Congressmen approved of this diffusion of responsibility. The enacted bill did not specify who would decide which drugs could only be sold with a prescription; it only stated that drugs that fell under the three categories listed above must be sold by prescription-only. President Truman

¹⁵⁶ Temin, *The Origin of Compulsory Drug Prescriptions*, 19.

signed the Durham-Humphrey Amendment into law on October 26, 1951.¹⁵⁷ The FDA took control over the enforcement of this amendment.

The Durham-Humphrey Amendment created two categories of drug products: prescription drug products and nonprescription drug products. The law labeled all products containing habit forming drugs and drugs unsafe for use without the supervision of a licensed physician as a prescription drug products. The state could now charge any person selling a prescription drug product without a prescription with the sale of a misbranded drug under the FDCA. This amendment also prohibited pharmacists from refilling prescriptions without the instruction of a physician. The passage of this amendment by Congress represents a victory for the FDA.¹⁵⁸ The FDA overcame drug industry lobbyists, including both pharmaceutical companies and proprietary medicine firms, in ensuring the passage of the amendment. The Durham-Humphrey Amendment represents the first federal law to regulate the use of nonnarcotic drug products by the public and physicians. The amended FDCA allowed the government to prevent the public from purchasing and consuming certain drug products.

The National Association of Retail Druggists (NARD) supported this piece of legislation because it protected retailers by reducing the likelihood that they would be faced with misbranding charges that resulted from inconsistencies in firms' classification of prescription drugs products.¹⁵⁹ Without the bill, retailers could be charged with misbranding for accidentally selling a prescription-only product without

¹⁵⁷ *The Durham Humphrey Amendment*. Public Law 215. *U.S. Statutes at Large* 65 (1951): 648-649.

¹⁵⁸ Carpenter, *Reputation and Power*, 152.

¹⁵⁹ Temin, *The Origin of Compulsory Drug Prescriptions*, 19.

a prescription; this bill could reduce such instances. The NARD worked with Congress to write the final bill. Drug manufacturers and the APhA opposed this bill initially because it empowered the FDA to decide which products could only be sold with a prescription, a power previously held by drug firms and pharmacists. The APhA ultimately supported the enacted bill, which removed the clause specifically empowering the FDA to create a list of prescription-only drug products, because they perceived the need to standardize prescription practices in any manner possible.¹⁶⁰

The APhA played a large role in changing the content of the bill concerning prescription refills. Congress removed clauses that would have barred pharmacists from refilling any prescription without re-consulting the physician.¹⁶¹ The enacted bill allowed physicians to instruct pharmacists to refill prescriptions either in the original prescription or orally. The AMA played very little role in the debate or passage of this amendment, even though the bill empowered the physician by mandating the necessity of physicians' prescriptions for the sale of numerous drug products.

Conclusion

This chapter has followed the development of the scientifically driven pharmaceutical industry in the 1940s. Despite the wishes of the FDA and AMA, the FDCA allowed for the sale of drug products that had been developed without FDA accepted scientific standards into the 1950s. In the 1940s, pharmaceutical firms such as Eli Lilly, Merck, Sharpe and Dohme, Pfizer, Bristol-Myers, Upjohn, Parke-Davis,

¹⁶⁰ Swann, "FDA and the Practice of Pharmacy," 60.

¹⁶¹ Robert Fischelis, oral history by James Harvey Young, The FDA Oral History Series, September 17, 1968, The FDA History Office, Rockville, MD, 110.

and Squibb, all expanded in size and scope. They hired large numbers of pharmacologists, chemists, and doctors to take part in the drug production process.¹⁶² Government officials pressured these firms to aid the military effort during World War II, which contributed to the speed with which companies developed and produced new drugs. Government sponsorship increased the pace of research on new drug compounds, specifically penicillin, and on drug production methods. Commercial pharmaceutical companies gained the capacity to manufacture drugs on an unprecedented scale.¹⁶³ These companies also produced increasingly therapeutically effective drug products, especially anti-infective agents.

In the 1940s physicians endorsed the use of drug products containing insulin, penicillin, and streptomycin enough to warrant Congress's establishment of certification programs for these products. Physicians endorsed and prescribed these products because they believed them to be effective agents in treating and curing diseases. The emergence of effective drugs during the 1940s also prompted Congressmen to pass the Durham-Humphrey Amendment. FDA administrators believed that certain effective drugs, including penicillin and streptomycin, could only cure disease if used under the supervision of a physician. Congressmen supported this belief and hoped to reduce the incidence of pharmacists and retailers selling drugs labeled for prescription-only use without a prescription. Furthermore, Congressmen recognized that using these drug products under physicians' supervision could improve the public health.

¹⁶² Carpenter, *Reputation and Power*, 112-115, 664.

¹⁶³ Adams, "Wartime Bureaucracy and Penicillin Allocation."

With the passage of the 1951 Amendment, the government standardized which drug compounds pharmacists could sell only with a physician's prescription. The NARD played a significant role in writing and passing this amendment. The passage of the Durham-Humphrey Amendment represents the first time that legislators changed the content of the FDCA in a manner that affected all drug manufacturers. The Penicillin and Insulin Acts, while important for the future of efficacy testing, affected only a portion of drug marketers. The Durham-Humphrey Amendment elaborated upon the law's previously vague stance on regulating physician's prescribing practices. While the introduction of the sulfa drugs prompted the passage of the FDCA in 1938, the emergence of effective cures used consistently by physicians prompted the passage of the first amendments to the FDCA in the 1940s.

At the end of 1951, the federal government regulated more stages of the drug production process than at any other previous point in history. The FDA governed how drug companies manufactured certain drugs, labeled all drugs, and how physicians, pharmacists, and the public used drugs for medical purposes. This authority would only increase over time. Congress passed the Durham-Humphrey Amendment just as Crawford replaced Dunbar as Commissioner of the FDA. Dunbar had treated Congress with a high level of respect and had succeeded in passing legislation and securing funds for the FDA. FDA employees considered Crawford's relationship with Congress much less congenial, which would become an issue in the early 1950s as the FDA struggled with limiting funding.¹⁶⁴

¹⁶⁴ Rankin, 50-57.

In the 1950s firms developed and sold record numbers of new drug products, most of which were tested in clinical trials before their distribution. The Durham-Humphrey Amendment required physicians' prescriptions for the distribution of drugs for investigational use before the FDA approved their NDAs. In the 1950s investigational drug use increased as researchers began depending progressively more on the results of clinical trials to determine the safety and efficacy of drug products. FDA administrators and medical officers encountered regulatory issues with the use of investigational drugs. The next chapter will discuss the conflict between health professionals, legislators, patient lobbyists, and the FDA on the initial testing of drugs in humans and the legal definition of drug efficacy.

Chapter Three: Regulating the Development of Drug Products: 1952-1963

Introduction

By 1951, the FDCA and its amendments empowered the FDA to regulate the mass-production, labeling, retail sale, and use of drug products; however, the FDA was not authorized to fully regulate drug development. Before 1962, the federal government regulated only a small part of the drug development process, by requiring proof of safety for new drug products. They did not regulate the efficacy of new drug products or how firms determined their safety. As discussed in Chapter Two, the FDA attempted to link the safety and efficacy of drug products during the 1940s. While they could not refuse NDAs based solely on a product's ineffectiveness, provided that it was not toxic, the FDA tried to remove ineffective products from the market by claiming that they had been mislabeled. During the 1950s, the FDA reorganized and stiffened the requirements for the New Drug Application process. Medical officers of the FDA's Bureau of Medicine changed the NDA form by requiring companies provide more data on therapeutic results of clinical trials and on the contents of their products.¹⁶⁵ This chapter demonstrates that the FDA attempted to compel firms to use contemporaneous scientific knowledge and techniques to develop drug products even though the law did not require this. Despite their efforts, federal legislation still only required proof of safety and allowed for unfettered investigational drug use.

¹⁶⁵ U.S. National Archives and Records Administration. *Federal Register* 20, no. 175 (1955); Carpenter, *Reputation and Power*, 157.

In the 1950s, FDA administrators came to believe that the federal government should regulate the development of drug products more strictly. I claim that they came to this realization because of the extent to which physicians, researchers, and drug firms distributed investigational drugs for public use.¹⁶⁶ While the FDCA required that firms provide evidence of the safety of new drug products, it did not specify how firms should investigate drug safety. The law permitted companies to distribute drug products to physicians without restriction if they were labeled “For Investigational Use Only.” In the 1940s and 1950s, investigational drug use could imply limitless types of experimentation on patients. While some firms organized formal large-scale clinical trials to investigate drug safety and efficacy, other firms distributed their products to practicing physicians, who then provided patients with appropriate ailments with the drugs and observed the results informally. In the 1950s, the investigational use of two drug products illustrated that this system did not reliably protect the health of patients.

The investigational use of Krebiozen and Kevadon (the brand name of the American thalidomide drug product), demonstrated the potential hazards of investigational drug use for the public health to FDA officials. The same medical officer at the New Drug Branch of the FDA’s Bureau of Medicine reviewed applications for both Krebiozen and Kevadon. This officer, Frances Oldham Kelsey, believed that Krebiozen, a product branded as a cancer cure, was ineffective, but the

¹⁶⁶ In this chapter I use the term “investigational drugs” rather than investigational drug products. I do so firstly because this is the terminology used by the FDA and legislators at the time. Also the researchers using investigational drugs are still developing these entities, and they have not yet been turned into products on the market.

FDA could not prevent its manufacturers from distributing the product for investigational use. Krebiozen became very popular, especially among unconventional medical practitioners. FDA officials perceived that the investigational use of ineffective drug products, like Krebiozen, was dangerous because they were used instead of conventional medical treatments. Researchers' continued investigational use of this product, despite the FDA's rejection of its NDA, demonstrated the need to regulate the early stages of drug development to FDA officials. Kelsey became renowned for her role in preventing the sale of Kevadon, which contained thalidomide, to the public. Thalidomide was an effective sedative drug, but was rejected by the FDA because of serious safety concerns. Eventually, overseas researchers discovered that thalidomide was unsafe for pregnant women, but not before thousands of children were born with severe birth defects. American physicians provided patients with thalidomide to investigate its effectiveness, causing birth defects in at least seventeen American children. Kevadon demonstrated the public health hazards that resulted for unregulated investigation drug use for the case of unsafe drug products to Congress and the American people.

This chapter argues that researchers' investigational use of Krebiozen and Kevadon and the public's response to these products convinced FDA officials and legislators of the need to regulate the development of drug products more rigorously. The public's support for Krebiozen, despite the FDA's opposition to its use, prompted the FDA to call for new legislation that would allow them to prevent the investigational use of products whose NDAs they had rejected. The public outcry

over the unknown dangers of Kevadon accelerated the passage of new investigational drug rules.

In addition, these products both advanced the FDA's demands for legislation requiring firms to prove the effectiveness, as well as the safety, of all new drug products. While the FDA had attempted to require drug firms to sell only effective products by removing ineffective products from the market, this strategy was faulty and numerous ineffective drug products were sold in the 1950s. Furthermore, allowing unrestricted investigational drug use meant that the FDA had no power to regulate an entire section of the drug market. These issues reached a climax in 1962, when overseas reports on thalidomide researched the United States.

Establishing Standardized Scientific Procedures to Develop Drug Products

Developments in pharmacology, the study of the composition and action of drugs in the human body, and in medical researchers' methods of performing clinical trials changed the way in which firms produced drug products in the 1950s. In turn, these changes in drug production methods prompted changes in federal legislation regulating this process by allowing for the creation of novel products. Academic and commercial drug researchers began to accept pharmacology as a discipline in the 1940s. Drug companies and academic researchers' extensive use of pharmacological theories devoted strictly to determining the impact of drug compounds on the human body illustrates that the government's use of science to regulate drug products mirrored the increased use of science firms' production of drug products. These developments complicated the drug development process and created a large influx of

drug products onto the American market in the 1950s, including Krebiozen and Kevadon, which will be discussed in later sections.

The Acceptance and Growth of Pharmacology in the 1950s

Pharmacologists are trained in the fields of chemistry, biology, physics, and medicine to be able to determine the impact of specific therapeutics on humans.¹⁶⁷ Clinical pharmacologists conduct animal tests and clinical trials to assess the impact of drugs *in vivo*, while other pharmacologists perform chemical assays to determine the composition of drugs. Pharmacology's importance for the FDA grew after the 1940s, as evidenced by their hiring of Dr. Ralph Smith, a doctor of pharmacology, to lead the New Drug Division of the FDA's Division of Medicine in 1950.¹⁶⁸ Both the FDA and pharmaceutical companies embraced pharmacology in the 1950s as their primary means of determining drug efficacy and safety. In 1955, the W.B. Lippincott House published the first comprehensive textbook in the field, *Essentials of Pharmacology*.¹⁶⁹ This demonstrates that the field was gaining in importance and status as an independent discipline.

At the same time that the FDA embraced pharmacology as a means to assess drugs, the National Institutes of Health (NIH) increasingly supported the execution of pharmacological studies. NIH performed and sponsored clinical trials of a new form embraced by pharmacologists in the late 1940s and the early 1950s.¹⁷⁰ Researchers

¹⁶⁷ Mannifred A. Hollinger, *Introduction to Pharmacology* (New York: CRC Press, 2003), 5.

¹⁶⁸ Smith, Checchi, Goldhammer, 1. Carpenter, *Reputation and Power*, 125-128.

¹⁶⁹ Frances O. Kelsey, Frances Oldham, and E.M.K Geiling, *Essentials of Pharmacology* (Lippincott: Philadelphia, 1955).

¹⁷⁰ Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990* (New York: Cambridge University Press, 1997); Donald

performed these new trials with a comparatively large number of patients at multiple clinical sites, randomizing the treatment groups and preventing both patients and doctors from knowing the treatment path of individuals. Pharmacologists had confidence in these double blind, multi-site, randomized clinical trials because they believed the protocols would produce more thorough and widely applicable data than would smaller trials.

Historian Harry Marks chronicles the history of the randomized clinical trial in *The Progress of Experiment*.¹⁷¹ Marks claims that the cooperative studies conducted by the Veteran's Administration (VA) and the Public Health Service were precursors to the randomized clinical trials that developed in the 1950s and 1960s. Marks argues that physicians and other researchers resisted the standardization of clinical trials during this time. Much of this resistance originated from physicians' desire to maintain physician-patient confidentiality. He also considers the growing impact of statistics on the assessment of clinical trials in the 1950s. Crucially, Marks' work demonstrates that the development of clinical trials in the 1950s affected more than just drug developers and pharmaceutical companies. Randomized clinical trials became significant methods of scientific experimentation debated, performed, and critiqued by numerous sectors of society. These included pharmaceutical industry employees, pharmacologists, academic researchers, physicians, patients, and lawyers.

Mainland, "Notes from a Laboratory of Medical Statistics," Freis Papers, NLM, B18 F19; "Protocol for Study of the Treatment of Infectious Hepatitis at the U.S. Army Hospital, Kyoto, Japan, January 1, 1952," Chalmers Papers, NLM, B36 F15; Thomas Chalmers, et. al., "The Treatment of Acute Infectious Hepatitis," *Journal of Clinical Investigation* 34 (1955): 1163-1235; Veterans Administration Cooperative Study on Antihypertensive Agents, "A Double Blind Control Study of Antihypertensive Agents," *AMA Archives of Internal Medicine* 106 (1960): 81-96.

¹⁷¹ Marks, *The Progress of Experiment*, Part II.

Despite the initial resistance of some physicians, the randomized controlled trial became the norm for performing medical research.

Developing the Randomized Clinical Trial: The Kyoto Study

Two major trials illustrate the methods and goals of clinical trials as the American government, academic researchers and pharmaceutical companies defined them in the 1950s: the Kyoto Hepatitis Study and the VA Cooperative Study on Hypertension.¹⁷² These trials, which became models on which other researchers organized clinical research on drug safety and efficacy, used large numbers of human subjects and took place over long periods of time. In the 1950s, pharmacologists in academic, commercial, and government settings came to define the ideal clinical trial as randomized, double blind, placebo-controlled, and multi-institutional.

Subsequently, greater numbers of patients were exposed to investigational drugs for longer amounts of time. Organizers of double-blinded clinical trials did not inform trial participants in or their doctors of their treatment route. In the 1950s firms performed more studies on human subjects and used more human subjects in trials than in the past. American pharmaceutical companies introduced more than double the number of new drug products in the 1950s than they did in the 1940s. Paul de Haen's "Compilation of New Drugs" states that drug firms worldwide introduced 202 new drug entities in the period from 1940 to 1949 and 421 new drug entities in the period from 1950 to 1959. This meant that pharmaceutical companies not only used

¹⁷² The details of Dr. Chalmers Hepatitis Study and Dr. Freis' VA Cooperative Study on Hypertension were both retrieved from their public collections at the National Library of Medicine in Bethesda, Maryland.

more human subjects in clinical trials, but also that these companies performed more clinical trials on new chemotherapeutics.

The privately and publically funded Kyoto Study on Hepatitis developed novel methods of performing clinical trials that used large numbers of patients. The Kyoto Study involved 460 participants. Although this trial did not assess the therapeutic value of drugs, it displays how researchers at the forefront of medical science performed clinical trials circa 1950. In 1951, the Epidemiological Board of the United States Armed Forces, the Office of the Surgeon General, the Commission of Liver Disease, and Harvard Medical School collaborated to conduct clinical trials based in Kyoto, Japan on the treatment of hepatitis. The Korean War, which lasted from June of 1950 until July of 1953, brought hundreds of thousands of American soldiers to the Asiatic region, many of whom developed acute infectious hepatitis. Dr. Thomas Chalmers led a group of civilian and army physicians to perform a study on non-chemotherapeutic treatments for hepatitis at the U.S. Army Hospital in Kyoto; these treatments included a high-protein diet, strict bed rest, and moderate physical activity.¹⁷³ They found that hepatitis patients improved more rapidly while eating a high calorie and high protein diet than while eating a normal diet and equally as well when kept active or confined to bed rest.

The Kyoto Study was significant for its use of statistical interpretation and its consideration of “doctor and ward effects.”¹⁷⁴ The Kyoto Study took place at one location, the US Army Hospital in Kyoto, but eight doctors on different wards

¹⁷³ Letter from Thomas Chalmers to Capt. James P. Worden, February 1, 1952, Chalmers Papers, B35 F16; Chalmers, et. al., “The Treatment of Acute Infectious Hepatitis,” 1164.

¹⁷⁴ Chalmers, et. al., “The Treatment of Acute Infectious Hepatitis,” 1209.

managed patients in the study. Chalmers, the lead author on the study's publication, acknowledged that physicians' preferences could be detrimental to clinical trials by affecting the objectivity of the results. Even though this specific study could not have been double-blinded, Chalmers raised concerns about researchers' biases and the influence of small changes in protocol on the final results. Through the 1950s, researchers performed increasingly more "double-blinded" clinical trials on drug efficacy.

By the early 1950s, both the government and academic institutions began to endorse the use of increasingly complex, lengthy, and detailed clinical trials in medical research, as shown by the joint private-public funding of the Kyoto study.¹⁷⁵ Pharmacologists at pharmaceutical companies also increasingly performed experiments with animals to assess drug safety before clinical trials. Overall, medical researchers more conclusively defined "the clinical trial" and more universally performed clinical trials in the 1950s. That is, randomized, controlled, double-blinded trials became the industry norm.

The standardization of how firms were expected to perform clinical trials allowed the FDA to implement strict regulations of investigational drug use in 1963. While it may seem counterintuitive that standardization within the industry would prompt regulations, standardization meant that the majority, not all, of pharmaceutical firms developed drug products using these types of clinical trials. By codifying these practices, the government could ensure that all companies consistently used clinical trials to establish the safety and efficacy of drug products.

¹⁷⁵ Carpenter, *Reputation and Power*, 159 n.62.

The 1959 VA Cooperative Study on Antihypertensive Agents signifies the completion of the transition in medical research to a uniformly scientifically acceptable clinical trial method. The VA Cooperative Study was one of the first randomized, double blind, placebo-controlled, and multi-institutional clinical trials performed to assess drug efficacy.¹⁷⁶ Cardiologist Dr. Edward Freis organized the study, which concluded that specific thiazide diuretic drugs could reduce hypertension.¹⁷⁷ This study, which continued through the 1960s, took place at eight hospitals, studied over four hundred participants, and assessed the merits of four different drugs at different dosages.¹⁷⁸ Researchers concluded that the drugs reserpine, mecamylamine, chlorisondamine, and pentolinium all reduce blood pressure in men with hypertension.

Codifying a New NDA Form: The FDA in 1955

In the 1950s the FDA not only preferred conventional pharmaceuticals to proprietary medicines, but also preferred certain rigorously and scientifically developed products to those developed without these methods. The FDA displayed its preference for drug products developed through the use of established chemical and biological assays, animal testing, and the new randomized, blinded, large-scale clinical trials through its public statements and NDA approvals.¹⁷⁹ Categorically, the

¹⁷⁶ “The Edward D. Freis Papers,” Profiles in Science: National Library of Medicine, <http://profiles.nlm.nih.gov/ps/retrieve/Narrative/XF/p-nid/172>, accessed February 22, 2012.

¹⁷⁷ Edward Freis, Oral History Interview by the Cortlandt Group, 1996, Freis Papers, NLM, B9, F3.

¹⁷⁸ Veterans Administration Cooperative Study on Antihypertensive Agents, “Double Blind Control Study of Antihypertensive Agents,” *Archives of Internal Medicine* 110 (1962): 222-229.

¹⁷⁹ Carpenter, *Reputation and Power*.135-137.

FDA disapproved of the products of the homeopathic and patent medicine industry (which existed by that name into the 1960s).¹⁸⁰ In the 1950s the methods of drug production preferred by the FDA's Bureau of Medicine became more clearly defined than they had been in the 1930s and the 1940s. I argue that the FDA began considering these rules because of the size of the growing pharmaceutical industry and the diversity in the types of drug products they sold. In the United States, the Executive Branch codifies the rules established by the executive departments and agencies of the government in the Code of Federal Regulations (CFR).¹⁸¹ FDA administrators codified new rules specifying the information required by the FDA for firms submitting NDAs to encourage their use of clinical trials and pharmacology.

Physicians' use of sulfa drugs, penicillin, streptomycin, and other anti-infective agents of the 1940s decreased the number of deaths caused by acute infectious diseases in America. The average lifespan of Americans increased by 4.4 years from 1930 to 1940 and again by 4.5 years from 1940 to 1950.¹⁸² The American Center for Disease Control has attributed this increase to numerous improvements in public health, including the use of vaccines, safer food products, the development of a public health system, and the introduction of antibiotics like penicillin and streptomycin.¹⁸³ By the 1950s, during which Americans' average life span increased

¹⁸⁰ Carpenter, *Reputation and Power*, 100-104, 425-426.

¹⁸¹ "Code of Federal Regulations," National Archives and Records Administration, accessed March 5, 2012, <http://www.gpoaccess.gov/cfr/>.

¹⁸² Arias, "United States Life Tables, 2006," 25-28.

¹⁸³ CDC, "Achievements in Public Health, 1900-1999: Changes in the Public Health System," *Morbidity and Mortality Weekly Report* 48 no. 50 (1999): 1141-1147; CDC, "Achievements in Public Health, 1900-1999, Impact of Vaccines Universally Recommended for Children -- United States, 1990-1998," *Morbidity and Mortality Weekly Report*, 48 no. 12 (1999): 243-248; CDC, "Achievements in Public Health,

by less than two years, antibiotics had become entrenched in conventional medicine. Firms continued to produce massive quantities of anti-infective agents and profited from these products.

In the 1950s, drug firms introduced more new drug products onto the American market than any other decade in American history. While the majority of the drug products introduced in the 1940s and in the 1950s were anti-infective agents, firms also introduced completely new types of drugs. The success of the antibiotics meant that the largest threat to American lives in previous decades—infectious diseases—had been controlled. Drug companies could then focus on other diseases troubling Americans and developed new types of drug products to treat chronic diseases (hypertension and cancer), mental illnesses (depression and anxiety), and other health issues (insomnia and obesity).¹⁸⁴ In 1949 the company Commercial Solvents introduced the first drug for treating high cholesterol, Inositol. In 1950 Merck began selling the first cancer chemotherapeutic, Mustargen, and Squibb introduced the first anti-arrhythmic cardiovascular drug, Gitaligin.¹⁸⁵ In 1954 Smith, Kline & French began selling the first tranquilizer drug, Thorazine; and in 1956 Geigy introduced the first non-amphetamine anti-obesity drug, Preludin.¹⁸⁶ In the 1950s firms not only increased the quantity of drug products they produced, but also increased the types of drug products they produced. In 1959 the research and

1900-1999: Control of Infectious Diseases,” *Morbidity and Mortality Weekly Report* 48 no. 29 (1999): 621-629.

¹⁸⁴ de Haen, “Compilation of New Drugs, 1940 Thru 1975.”

¹⁸⁵ Mustargen (mechlorethamine), the first chemotherapeutic developed for the purpose of treating cancer, is an analog of mustard gas, a highly toxic poison used in WWII trench warfare. This drug is still in use today.

¹⁸⁶ de Haen, “Compilation of New Drugs, 1940 Thru 1975,” 40.

development expenditures of ten major companies increased from \$167,300,000 to \$617,500,000, almost a four-fold increase.¹⁸⁷

The number and complexity of new drug products introduced in the 1950s, along with the new forms of drug development prompted FDA officials and legislators to consider strengthening the federal pre-market approval process for drug products by requiring firms to prove drug efficacy in NDAs. While the FDA's Bureau of Medicine had attempted to indirectly regulate the efficacy of drug products by removing ineffective products from the market and rejecting NDAs since the 1940s, the fact that the law did not require firms to prove the efficacy of new drug products became increasingly problematic as firms produced more lifestyle drugs.¹⁸⁸ In producing a wider variety of drug products, firms complicated the definitions of drug safety and efficacy. Determining the efficacy of lifestyle drugs, like sleep aids and mild anti-anxiety products, was more difficult to determine than determining the efficacy of anti-infective drug products.

The FDA established procedures and protocols for enforcing the FDCA that reflected their confidence in scientific methods of testing drug safety and efficacy in the late 1940s and the 1950s. In 1955 the FDA successfully proposed amending the Code of Federal Regulations to include a new form of the New Drug Application specifically requiring the inclusion of "any adverse affects and therapeutic results

¹⁸⁷ Ralph Smith, Basil Achilladelis, and Alexander Scriabine, ed., *Pharmaceutical Innovation: Revolutionizing Human Health* (Philadelphia: Chemical Heritage Foundation, 1999), 77. The firms used for this data were Abbott, Bristol-Myers, Eli Lilly, Merck, Parke-Davis, Pfizer, Schering-Plough, Searle, Smith Kline and French, and Upjohn.

¹⁸⁸ Carpenter, *Reputation and Power*, 149-156.

observed” in a drug’s analysis.¹⁸⁹ While the new form did not require firms to prove the efficacy of new drug products, it required firms to include all efficacy information about the products in the NDA. I argue that the increase in the number of type of products sold by the pharmaceutical industry prompted FDA administrators to codify this new NDA form by demonstrating researchers’ increasingly complex understanding of drug safety and its connection to efficacy. Although actual impact of the new NDA form is unclear, its implementation clearly illustrates the significance of scientific standards and proof for FDA officials reviewing the therapeutic merit of new drug products.

The increase in the types of products of the pharmaceutical industry also brought large profits to the industry. As discussed in Chapter Two, the popularity of penicillin in the mid-1940s demonstrated to drug companies that prescription drug products could be hugely profitable. By the 1950s, drug companies developed new ways of profiting from prescription drug sales, and the pharmaceutical industry earned higher profits than any other American industry.¹⁹⁰ One of the major ways they earned profits was by introducing “me-too” drugs, products that differed only slightly from those already on the market, but that firms advertised as novel.¹⁹¹ Pharmaceutical firms produced numerous anti-infective “me-too” drugs in the 1950s. In 1949 10.8 percent of physicians’ prescriptions were for anti-infective agents; by

¹⁸⁹ Federal Register, 21 (143) (July 25, 1956): 5578; Carpenter, *Reputation and Power*, 157-160.

¹⁹⁰ “Pricing Policies of Drug Industry,” *Congressional Record*, 86th Congress, 2nd sess., January 22, 1960,

¹⁹¹ Harry Dowling, “Statement Before Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, of the U.S. Senate, September 14, 1960,” Dowling Papers, NLM, B10 F “Kefauver Legislation”.

1960, this number doubled to 23.3 percent.¹⁹² Some medical professionals believed that many pharmaceutical firms had become overly interested in financial gains. In 1961, a former industry medical director said of the drug industry:

Industry spokesmen would have us believe that all research is on wonder drugs or better medicinal products. They stress that there are many failures for each successful drug. This is true... The problem arises out of the fact that they market so many of their failures... Most [industries] must depend on selling only their successes... [But] with a little luck, proper timing, and a good promotion program a bag of asafetida with a unique chemical side chain can be made to look like a wonder drug. The illusion may not last, but it frequently lasts long enough. By the time the doctor learns what the company knew at the beginning it has two new products to take the place of the old one.¹⁹³

This anonymous medical professional believed that some drug companies produced new drug products that were not therapeutically novel, or even effective, simply to profit from their sales. Despite criticisms from medical professionals for this tactic, pharmaceutical sales increased through the decade

Technical developments in pharmacology and medical research allowed for the production of more and diverse drug products, which complicated the concepts of drug efficacy and safety. As a result, the FDA introduced a new NDA form that required firms to submit efficacy data from their investigations (but not necessarily proof). This measure demonstrates that the FDA wanted to be able prevent the sale of ineffective drug products more easily. When Congress eventually began considering

¹⁹² Arthur D. Little, Inc., “A Report on the Aspects of Concentration and Product Obsolescence in the Pharmaceutical Industry in the United States,” (Cambridge, MA: Acorn Park, 1962), cited in Jeho Tee, “Innovation and Strategic Divergence: An Empirical Study of the U.S. Pharmaceutical Industry from 1920 to 1960,” *Management Science* 49 no. 2 (2003): 146-147.

¹⁹³ Senate Judiciary Committee 1961, 127, quoted in Sam Peltzman, “Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments,” *Journal of Political Economy* 81 no. 5 (1973): 1050.

to amend the FDCA in 1959, the FDA Bureau of Medicine argued first and most strongly for the requirement of “proof of efficacy” for all new drug products.

The Potential Public Health Hazards of Investigational Drug Use

Despite the introduction of a new NDA form, the FDA remained concerned about the actions of drug industry, and especially their distribution of drug products for investigational use. Without an amendment to the FDCA, however, the FDA could not limit investigational drug use. The popularity Krebiozen, a drug product that retained a substantial body of followers despite its rejection by the FDA, demonstrated the value of amending to FDCA to allow the FDA to prevent investigational drug use to FDA officials. Kevadon demonstrated that the investigational use of unsafe drugs could seriously harm the public health, especially since large scale clinical trials were becoming the norm. I argue that experiments on Krebiozen and Kevadon and the public’s response to these products intensified the FDA’s concern with unregulated investigational drug use and eventually compelled its officials to codify the exact manner in which firms could develop drug products.

Attempting to Remove Ineffective Cancer Drug Products From the Market: The FDA in the 1940s and 1950s

From the 1920s through the 1950s FDA administrators continued to concern themselves with the sale of drug products claiming to cure cancer that they believed had no medical or scientific basis to do so. These products were mostly safe, so FDA medical officers struggled to prevent their sale and remove them from the market. As noted in the previous section, Merck introduced the first drug product that claimed to

treat cancer in 1950, Mustargen. In the 1950s, pharmaceutical companies introduced a total of nine cancer chemotherapeutics, all of which physicians use to treat various types of cancer today.¹⁹⁴ The availability of effective, albeit dangerous and imperfect, cancer treatments likely caused FDA medical officers to further attempt to prevent the sale of ineffective cancer drug products, also referred to as “quack drugs”.

In the 1940s the FDA prosecuted the makers of two major cancer cures for mislabeling drug products with false therapeutic claims: Koch’s Cancer Cure and the Hoxsey Cancer Cure.¹⁹⁵ The makers of Koch’s Cancer Cure claimed that the product contained minute amounts of a revolutionary chemical that cured cancer called glyoxylyde. Koch Laboratories claimed to have used conventional scientific principles in developing and producing the Cure, but the FDA could not identify this compound, doubted their claims, and seized the product in 1942.¹⁹⁶ The makers of Hoxsey’s Cancer Cure would not initially reveal the contents of their product; they eventually conceded that the product contained only a mixture of botanicals, but still claimed its

¹⁹⁴ The National Library of Medicine’s online database “PubMed Health” contains entries for all of the drugs introduced onto the market in the 1950s to treat cancer. These include: Mustargen (mechlorethamine HCl), aminopterin sodium, Purinethol (mercaptopurine), Myleran (busulfan), triethylenemelamine, methotrexate, Leukeran (chlorambucil), Cytosan (cyclophosphamide), and thio-tepa.

¹⁹⁵ Federal Security Agency, Food and Drug Administration, “2534. Alleged misbranding of Glyoxylyde, Benzoquinone, and Malonide” Notices of Judgment Under the Federal Food, Drug and Cosmetic Act, 2500-3000 (1949): 194, accessed 18 January 2012, <http://archive.nlm.nih.gov/fdanj/handle/123456789/11373>; Federal Security Agency, Food and Drug Administration, “3288. Misbranding of Cancer Cure,” Notices of Judgment Under the Federal Food, Drug and Cosmetic Act, 3000-3500 (1951): 260, accessed January 26, 2012 <http://archive.nlm.nih.gov/fdanj/bitstream/123456789/11986/3/ddnj03288.pdf>.

¹⁹⁶ Richard E. McFadyen and James Harvey Young, “The Koch Cancer Treatment,” *The Journal of the History of Medicine and Allied Sciences*, 53, (1998): 268.

efficacy.¹⁹⁷ Similarly, the FDA seized the Hoxsey product and prosecutors charged the company with mislabeling. This was a part of the FDA's goal to remove unconventional drug products from the market; including those that they believed incorrectly used conventional scientific methods and those that ignored conventional scientific methods. Prosecutors struggled to actually convict the makers of these products with mislabeling, but they eventually lost popularity because of negative publicity.

In a 1986 interview, William Goodrich, a federal lawyer with the Food and Drug Division from 1939 until 1971, declared that the most difficult part of prosecuting a firms for marketing an alleged ineffective cancer cures in the 1940s and 1950s was proving ineffectiveness when the defense presented witnesses who claimed the product cured them.¹⁹⁸ He claimed that cancer is such a complicated and misunderstood disease and that, "people somehow want to believe [in the drug's efficacy]." During the 1950s the FDA continued to struggle with prosecuting cases against firms that sold drug products they believed were ineffective, and administrators began to push for legislative change.

Opposing Investigational Drug Use: Krebiozen and the FDA

The FDA's difficulty in prosecuting the makers of the Hoxsey and Koch Cures did not directly prompt legislative changes to the FDCA because the public mostly rejected these products after the FDA had prosecuted them. Their makers did

¹⁹⁷ Harry Hoxsey, *You Don't Have to Die* (New York: Milestone Books, Inc., 1956), 65-74.

¹⁹⁸ Goodrich, 46.

not continue to propagate their use beyond the 1940s.¹⁹⁹ Additionally, they were not introduced at a time when researchers had discovered effective cancer drug products. However, Krebiozen, another cancer cure in which the FDA lacked confidence, was introduced in the early 1950s, and its case displays the reasons why FDA administrators pushed for legislators to further amend the FDCA to strengthen the pre-market approval process and to restrict investigational drug use. A substantial portion of the American public became convinced of the merit of Krebiozen. This commercial success and public pressure to approve Krebiozen, despite the FDA's adamancy of the product's uselessness, motivated FDA Bureau of Medicine employees to call for immediate legislative change.

In the late 1940s a Yugoslavian physician, Dr. Stevan Durovic, developed a product, which would become known as Krebiozen in the United States. He claimed to have isolated a therapeutically effective compound from the blood of cattle that had been infected by a specific strain of bacteria.²⁰⁰ To make the compound suitable for human use, Durovic suspended the compound in mineral oil; he planned to inject the drug into patients. Durovic went to Chicago in 1949 to market the product. There, he sought out Dr. Andrew C. Ivy, then vice-president of the University of Illinois and established medical researcher, to support his venture. Durovic claimed to have cured cats and dogs of cancer in Argentina before beginning clinical trials in American in

¹⁹⁹ The "Hoxsey Herbal Treatment" continues to be used by some people today as a homeopathic cancer treatment, but it has remained a very minor product and is not sold as a "drug". The American Cancer Society recognizes it, but does not support its usage or claim it to be effective,
<http://documents.cancer.org/acs/groups/cid/documents/webcontent/002420-pdf.pdf>.

²⁰⁰ James F. Holland, "The Krebiozen Story," *Journal of the American Medical Association* 200 no. 3 (1967): 213.

1949.²⁰¹ Durovic convinced Ivy of the potential therapeutic merit of his product, then called Substance X, and the two began performing clinical trials at Chicago area hospitals in August of 1949.²⁰² By 1951, Ivy had had a lengthy career in medicine, working at the AMA, the Naval Medical Research Institute, and several academic institutions. He had been well respected throughout the profession, but his support of Krebiozen prompted physicians and medical researchers to question his judgment.²⁰³

Before beginning large scale, complex clinical trials, most drug developers performed initial tests in humans to establish the possibility that a drug could have therapeutic value. Durovic and Ivy aimed to establish evidence that displayed the therapeutic effectiveness for the substance, now known as Krebiozen, with their initial trials in 1949 and 1950. They analyzed the effects of the drugs on individual cancer patients. On March 26, 1951, Ivy presented their findings from twenty-two patients to a conference of medical professionals and the media in Chicago.²⁰⁴ Ivy announced that they had found Krebiozen to have high potential for treating cancer and promoted its investigational use. In doing so Dr. Ivy violated the code of the Chicago Medical Society and they immediately revoked his membership. The Code maintained that physicians could not directly propagate a commercial drug product because such financial involvement limited the physicians' objectivity in prescribing

²⁰¹ Stevan Durovic, "Cancer and Krebiozen: A New Concept in Cancer," *Today's Japan, Orient/ West* 6 (1961): 51-55.

²⁰² American Cancer Society, "A Background Paper on Krebiozen," *Journal of the American Medical Association* 169 no. 15 (1959): 1791.

²⁰³ Fishbein, *The History of the AMA*, 48.

²⁰⁴ Holland, "The Krebiozen Story," 213; American Cancer Society, "Background Paper," 1792.

drug products.²⁰⁵ Ivy soon stopped paying dues to the Illinois Medical Society and the AMA, both of which also terminated his membership. The AMA Council on Drugs began investigating Krebiozen shortly after Ivy and Durovic began their own clinical trials.

The Council claimed that they took an interest in Krebiozen because they wanted to prevent the production of ineffective cancer treatments, as their availability dissuaded patients from undergoing treatment for cancer endorsed by the AMA. As discussed in Chapter One, the AMA endorsed medical practices and drug products developed with the use of conventional science; they did not believe that Krebiozen was a legitimate cancer treatment. The AMA had also historically scorned firms for producing drugs purely for profit.²⁰⁶ They consulted all available information on the drug and the experiments and concluded that the drug was ineffective in treating cancer. In August of 1951, the AMA notified Ivy that they would soon publish a report proclaiming the uselessness of Krebiozen and critiquing Dr. Ivy.²⁰⁷ This began the AMA's forceful opposition to the use of Krebiozen in treating cancer, during which Ivy continued to defend Krebiozen.²⁰⁸ The AMA's opposition to Krebiozen originated from the Durovic's refusal to inform any outside organizations of the chemical content of Krebiozen or the manufacturing procedures for producing Krebiozen.²⁰⁹ The AMA, along with the FDA, believed that the company had no

²⁰⁵ Holland, "The Krebiozen Story," 214.

²⁰⁶ Simmons "The Commercial Domination," 1644-1646.

²⁰⁷ Letter from Dr. Franklin C. Bing to Dr. Andrew C. Ivy, August 1, 1951, Kelsey Papers, LOC, B20 F7.

²⁰⁸ Letter from Dr. Andrew C. Ivy to Dr. Franklin C. Bing, August 6, 1951, Kelsey Papers, LOC, B20 F7.

²⁰⁹ Holland, "The Krebiozen Story," 217-218; American Cancer Society, 1797.

legitimate reason to refuse to provide outsiders with information on the manufacturing and contents of Krebiozen. Both organizations disapproved of such secretiveness for reasons of commercial profit. Durovic's reasons for not providing this information are not known, but the AMA and the FDA likely assumed that they knew the product was ineffective and did not want to allow the FDA to perform their own assessments of Krebiozen.

Durovic's company, Research Laboratories, submitted an NDA for Krebiozen in 1954, and again in 1961.²¹⁰ The FDA rejected the application on both occasions because the medical officers, especially Frances Kelsey, believed that the application lacked adequate information and because the firm refused to reveal the chemical contents of Krebiozen, or its methods of production. Specifically, Research Laboratories Inc., did not provide information on "original biopsy, autopsy, or x-ray reports, pre-surgical physical findings, and surgical procedures... blood studies, weight changes, etc. when these were pertinent."²¹¹

After 1954, Durovic and Ivy continued to distribute Krebiozen to doctors for investigational use without any legal responsibility to the FDA other than including "For Investigational Use Only" on Krebiozen's label. Durovic and Ivy founded the Krebiozen Research Foundation to supply and support doctors interested in Krebiozen research. The FDA's lack of control over investigational drug use permitted Krebiozen to become popular despite the objections of the FDA and the AMA. Ivy and Durovic convinced numerous members of the American public of the

²¹⁰Department of Health, Education and Welfare, Press Release June 7, 1963, Kelsey Papers, LOC, B20 F7.

²¹¹Frances Kelsey, "NDA 12-823 Krebiozen Summary 1961," Kelsey Papers, LOC, B20 F7, 6.

effectiveness of Krebiozen. The drug likely gained popularity throughout the 1950s because of Ivy's prominence. Although the AMA rejected Ivy's latest project, the Association highly regarded his previous work and he was well known publically. For example, when the prosecutors of the post-WWII Nuremburg Trials asked the AMA for a medical consultant in 1947, the AMA choose Ivy to serve as a trial consultant.²¹² During the trials Ivy became a prominent public figure, known for his extensive experience in medical research. When Research Laboratories resubmitted an NDA for Krebiozen in 1961, Kelsey, the primary medical officer assigned to the application, received dozens of letters demanding that the FDA accept the application.²¹³ The public vocally called for the approval of Krebiozen.

The FDA hired Kelsey, a pharmacologist by training, in 1961, just one year prior to the filing of Krebiozen's second NDA. Before working for the government, Kelsey taught pharmacology at the University of Chicago and the University of South Dakota, and authored a textbook in the field. Her extensive background in pharmacology likely contributed to her stringency in reviewing NDAs. The FDA came to oppose Research Laboratories because they believed that it developed the drug to make money, rather than to cure cancer patients. While the FDA accepted that drug companies profited from their products, they did not approve of firms producing ineffective drug products purely for profit. FDA administrators, including Director of

²¹² Jon M. Harkness, "Nuremberg and the Issue of Wartime Experiments on US Prisoners," *Journal of the American Medical Association* 276 no. 20 (1996): 1672.

²¹³ "An Open Letter to Congress", Letter from Janie A. Meeter to the Senators and Representatives of the United States Congress, September 16, 1963, Letter from Dorothy B. Coffman to Senators and Congressmen, September 16, 1963, Kelsey Papers, LOC, B20 F7, 6. The collection also contained dozens of more letters addressed directly to Kelsey and the FDA asking for the allowance of Krebiozen research and use in the late 1950s and early 1960s.

Pharmaceutical Sciences Dr. Daniel Banes, believed that the sponsors of Krebiozen intentionally deceived the American people in promoting the effectiveness of Krebiozen.²¹⁴

The actions of Research Laboratories prompted FDA officials to act on their belief in the need to amend the FDCA by adding regulations on both the development and the investigational use of drugs. Although Research Laboratories performed and reported on numerous small-scale clinical investigations, they provided very little basic chemical information about their product. The firm did not provide *in vitro* studies of the drug or summaries of animal testing, both of which the FDA aspired to legally require of all new drug products. The firm did not claim to understand the mechanism by which the drug cured cancer, a crucial tenet of pharmacology.²¹⁵ As much as the FDA attempted to restructure the NDA, firms could still attempt to produce and manufacture drug products in any manner they desired.

The Krebiozen case demonstrates that a drug firm could achieve popular support for a drug product despite the FDA's belief in the product's ineffectiveness. I suggest that the FDA and other medical professionals opposed the distribution of Krebiozen because it posed an indirect threat to the public health. Research Laboratories persuaded some patients to forgo conventional cancer chemotherapeutic treatment and take that Krebiozen instead, which may have caused patients to die.

²¹⁴ Daniel Banes, Oral History by James Harvey Young and Robert G. Porter, The FDA Oral History Series, June 17, 1980, The FDA History Office, Rockville, MD, 31-40.

²¹⁵ This is not to say that researchers in the 1950s understood the mechanism of how most drugs worked on the body. The FDA was more opposed to the fact that Research Laboratories had not attempted to determine the mechanism or the relationship between the structure of the chemical and its function in the body.

Because of this, FDA officials began to perceive the need for regulating drug products even before firms began to market them to the public. In the 1950s, the FDA recognized that the public had access to drugs even before firms put them on the market. Physicians could even act as advertisers for drug products not yet on the market. The FDA recognized that drugs were not just commercial products, but also investigational articles.

Investigating Thalidomide in the US and Abroad

While Krebiozen demonstrated the dangers of investigational use of ineffective drug products, another drug product, Kevadon, prompted the FDA to become concerned about the investigational use of unsafe drugs. Kevadon, often known by the name of the drug compound it contained, thalidomide, displayed the potential dangers of investigational drug use. Thalidomide emerged from the growing class of drug products on the market produced to alleviate ailments, rather than to treat diseases. German chemists discovered thalidomide in 1954 and recognized its potential use as a sedative to mitigate a range of ailments, including respiratory soreness, insomnia, and morning sickness in pregnant women.²¹⁶ By the end of 1961, researchers established that thalidomide caused serious birth defects in the children whose mothers consumed it. Pharmaceutical companies that manufactured thalidomide drug products responded to this information slowly; over 10,000 children were born with thalidomide-induced birth defects by 1962.²¹⁷ The first firm to develop a thalidomide drug product, the German pharmaceutical company Chemie-

²¹⁶ Harey Teff and Colin Munro, *Thalidomide: The Legal Aftermath* (Westmead, England: Saxon House, 1976), 1-10.

²¹⁷ Morton Mintz, "Heroine of the FDA Keeps Bad Drug Off of Market," *Washington Post*, July 15, 1962, A1.

Grünenthal, began marketing the product in Germany in October of 1957 as a sedative called Contegran. In 1958 drug firms from countries around the world developed thalidomide products, including firms in Great Britain, France, and Australia. Although this chapter has detailed the perceived faults of America's drug regulatory system, American pre-market regulations were stricter than those in any other country.

Animal testing of thalidomide products showed signs of dangerous side effects that warned off numerous American firms, and eventually resulted in the FDA's rejection of Kevadon's NDA. Despite this, investigational use of Kevadon in the U.S. persisted for three years. Grünenthal executives approached several American pharmaceutical firms about producing a thalidomide drug; these companies, including Smith, Kline and French, rejected the offer after performing initial animal tests.²¹⁸ In late 1958 the William S. Merrell Company agreed to market thalidomide in the United States. Merrel soon began distributing their thalidomide product, Kevadon, to physicians for investigational use. By August of 1962, over 1,200 physicians had administered thalidomide to almost 20,000 American patients.²¹⁹

Grünenthal marketed Contegran in Germany as a remarkably safe sedative through 1961, but the FDA New Drug branch doubted these claims.²²⁰ The rejection

²¹⁸ Trent Stephens and Rock Bryner, *Dark Remedy: The Impact of Thalidomide and Its Revival as a Vital Medicine* (Cambridge, MA: Perseus Publishing, 2001), 17.

²¹⁹ U.S. Department of Health, Education and Welfare, "Press Release on Thalidomide August 23, 1962", Dowling Papers, NLM, B10 F "Thalidomide".

²²⁰ Teff and Colin, *Thalidomide*, 2-4; *Congressional Record* (August 8, 1962) reprinted in John Lear, "The Unfinished Story of Thalidomide," *SR/Research*, September 2, 1962, 36-37.

of the Kevadon NDA indicates that, by the end of the 1950s, some FDA medical officers had come to expect extensive safety and toxicity testing for new drug products. The FDA New Drug Branch refused to accept Merrell's Kevadon NDA, submitted in September of 1960. Medical officers believed that the firm had not yet performed adequate safety or toxicity testing in animals or in humans. Dr. Frances Kelsey, who also rejected the application for Krebiozen, refused to accept the Merrell Company's application repeatedly. She stated:

The application is incomplete under section 505 (b) (1) of the act as follows: It fails to report the animal studies in full detail. The isotope study on absorption of the drug in rats cited in the brochure is not supported by the data in its application. It fails to report the clinical studies in full detail. The reports should include detailed information pertaining to each individual treated, including age, sex, conditions treated, dosage, frequency of administration, duration of administration of the drug, results of clinical and laboratory examinations made, and a full statement of any adverse effects and therapeutic results observed. Many of the cases reported in the application are in summary form without the necessary detail included. In addition, the application is inadequate under section 505 (b) (1) of the act in that insufficient cases have been studied.... The application is further inadequate...in that the chronic toxicity data are incomplete and therefore no evaluation can be made of the safety of the drug when used for a prolonged period of time... The statement furnished by Chemie Grünenthal pertaining to the manufacturing, processing, and control operations for the new-drug substance fails to fully describe the physical facilities including plant and equipment used: it also fails to state the methods and controls used to determine the identity, strength, quality, and purity of the new drug substance...²²¹

This lengthy excerpt cites only a fraction of the faults Kelsey found with Merrell's NDA for Kevadon. This letter illustrates Kelsey's background in pharmacology and her desire to ensure that the marketers of all new drug products performed the tests she believed necessary to proving drug safety. As discussed in Chapter Two, the FDA

²²¹ Letter from Dr. Kelsey to the Merrell Company, November 10, 1960, reprinted in "Thalidomide Chronology," *Drug Research Reports* 5 no. 36 (1962): 399-S.

did not strictly define “safety” and individual FDA medical officers used their own discretion in making this distinction. Kelsey believed in the necessity of basic chemical assays, animal testing for safety and efficacy, and human testing for safety and efficacy in NDAs. She also directly informs the company of the need to ensure the consistency (“strength, quality, and purity”) of manufacturing drug products.

The Merrell Company repeatedly pressured the FDA New Drug Branch to accept the drug. The FDCA mandated that the FDA had only sixty days during which to consider an NDA. After sixty days the law compelled the FDA to either accept or reject the NDA, or request more information from the firm. This meant that every sixty days from September of 1960 until March of 1962, the FDA informed Merrell Company that the Kevadon NDA was incomplete and that they considered the application resubmitted. During this period of time, the Merrell Company contacted the FDA’s Bureau of Medicine forty one times, while FDA officers contacted the Merrell Company only eleven times.²²² The two groups met twice to discuss the Kevadon NDA. Medical officer Dr. Frances Kelsey refused to accept Kevadon because of doubts surrounding its safety, especially in pregnant women. In November of 1960 she demanded more toxicity tests in animals and evidence of the drug’s safety in pregnant women and animals. A 1964 government report on thalidomide quotes Kelsey: “I was bothered by the fact that thalidomide would not put some of the test animals to sleep. Why would it induce sleep in human beings and not in the

²²² *Congressional Record* (August 8, 1962), reprinted in Lear, “The Unfinished Story of Thalidomide,” 36-37.

animals? It was a very unusual kind of drug and we had no idea how it worked.”²²³

Specifically, Kelsey informed Merrell that the NDA lacked adequate chronic toxicity testing, a sample of the product, acceptable proposed labeling, and testing on side effects of the product.²²⁴

Physicians around the world prescribed thalidomide drug products to patients as a sedative in large quantities from 1957 until late 1961. Barbiturates, the only conventional sedatives available before thalidomide, can be extremely addictive and physicians tried to avoid prescribing them without extreme necessity. Physicians distributed thalidomide to such an extent because it was a mild, non-addictive sedative without any known side effects.²²⁵ In 1959 researchers outside of the company informed Grünenthal that they had found evidence that thalidomide caused nerve damage and peripheral neuritis, the loss or change in one’s ability to feel bodily sensations.²²⁶ In December of 1960, the *British Medical Journal* published the first piece linking thalidomide to nerve damage. The editors continued to publish articles questioning the safety of thalidomide in 1961.²²⁷ By the end of 1960, the sharp increase in a specific type of birth defect, known as phocomelia, raised strong concerns among pediatricians and epidemiologists. Eventually, pharmacologists recognized that mothers who had taken Contegran and other thalidomide drug

²²³ Department of Health, Education and Welfare, “Reference Material: The Thalidomide Story,” February 1964, Kelsey Papers, LOC, B32, F8.

²²⁴ “Thalidomide Chronology,” 399-S.

²²⁵ Department of Health, Education and Welfare, “Reference Material: The Thalidomide Story,” Kelsey Papers, LOC, B32, F8.

²²⁶ Teff and Colin, *Thalidomide*, 2-4.

²²⁷ Florence A. Leslie, “Is Thalidomide to Blame?” *British Medical Journal* 5217 no. 2 (1960): 1954; Pamela Fullerton and Michael Kremer, “Neuropathy After Intake of Thalidomide,” *British Medical Journal* 5256 no. 2 (1961): 855-857; “Thalidomide Neuropathy,” *British Medical Journal* 5256 no. 2 (1961): 876-877.

products gave birth to most of the children born with phocomelia, a severe defect that causes malformed and missing extremities. In December of 1961, two physicians, William McBride and Widukind Lenz, independently published reports concluding that thalidomide caused phocomelia in the unborn children of women who took the drug.²²⁸ Though studies on the safety of thalidomide were not performed until 1955, by the late 1950s, medical professionals knew that nerve damage in pregnant women could cause fetal deformities.²²⁹ That is, the medical community could have predicted that thalidomide's association with nerve damage would be dangerous for the fetus even before cases of fetal abnormalities in Germany and Great Britain began rising in the summer of 1960.

Though medical researchers outside the United States continued to question to safety of thalidomide, American researchers did not appear to concentrate on the issue. The editors of the *Journal of the American Medical Association* and of the *New England Journal of Medicine* failed to report on any thalidomide research until 1962. The regulations of the FDCA effectively kept Kevadon off of the American drug market; however, the government did not know the extent of the investigational use of the drug. By the end of 1961 Grünenthal and other makers of thalidomide drug products in Europe withdrew the products from the market. In March of 1962, the Merrell Company officially withdrew its NDA for Kevadon. Even though the FDA never approved Kevadon in the United States, physicians gave the drug to about 20,000 patients for investigational use, including 200 pregnant women. At least ten

²²⁸ William McBride, "Thalidomide and Congenital Abnormalities," *Lancet* 2 (1961): 1358; Carpenter, *Reputation and Power*, 240 n18.

²²⁹ Teff and Colin, *Thalidomide*, 5.

mothers in America, and possibly another seven, gave birth to children with phocomelia because of thalidomide. This information is not definitively known because the government did not require firms to track investigational drug use. Even if firms kept such records, the FDA could not compel firms to disclose them. Some researchers have estimated that approximately 10,000 children were born worldwide with thalidomide-induced defects.²³⁰ The thalidomide events made FDA administrators more aware of two major shortcomings of the FDCA: its lack of restrictions on investigational drug use, and its lack of specifications about the performance of clinical trials and animal testing.²³¹

Strengthening Regulations on Drug Development and Introducing Regulations on Investigational Drug Use

The public concern with drug prices and the FDA's desire to regulate drug development converged in the late 1950s to spark regulatory change. Senator Carey Estes Kefauver began investigating the drug industry in 1959 because he questioned their pricing practices and hoped to enact legislation to reduce drug prices, given the high profits of the industry. Just as the deaths resulting from the Elixir Sulfanilamide prompted the passage of the FDCA in 1938, the thalidomide births propelled Kefauver's amendments to the FDCA through Congress in 1962. Unlike the deaths resulting from the use of the Elixir, though, most of the misfortunes that resulted from the use of thalidomide occurred outside of the United States. This fact did not reduce

²³⁰ Teff and Colin, *Thalidomide*, 4.

²³¹ George Larrick, "Current Federal Drug Controls for Problems Old and New," speech delivered at the Federal Wholesale Druggists' Association meeting, September 27, 1961, Dowling Papers, NLM, B10 F "Kefauver Legislation".

the fear of Congress and the American public regarding the dangers of an under-regulated drug industry. Congress and the FDA perceived more problems with the drug industry than the lack of sufficient scientific studies and controls on investigational drug use. Almost three years after Kefauver began officially investigating the drug industry in December of 1959, President John F. Kennedy signed the 1962 Drug Amendments into law. The Kevadon events ultimately shaped the manner in which the FDA proposed to amend the investigational drug use sections of the FDCA and pushed the bill through Congress.

Investigating Drug Pricing: Estes Kefauver and the Senate Antitrust and Monopoly Subcommittee

In December of 1959 the Senate Judiciary Committee's Antitrust and Monopoly Subcommittee initiated an investigation of the drug industry as part of their extensive inspection of organized pricing within various industries. Kefauver, a liberal Democrat from Tennessee who served in Congress from 1949 until his death in 1963, headed this Subcommittee. Political historians regard Kefauver to be one of the most authentic and successful political mavericks of his generation.²³² Throughout his political career, Kefauver fought against organized crime and monopolies in American industry. Kefauver believed strongly in the rights of the consumer and in protecting the public against profiteers. Kefauver initially began investigating the drug industry because he believed that drug firms sold their products for exorbitant

²³² Joseph Bruce Gorman, "Kefauver: A Political Biography," (New York: Oxford University Press, 1971), 3.

prices and wanted to reduce these prices through legislation.²³³ FDA administrators supported Kefauver's investigation and expressed their opinions about their own desires for drug development regulations. The FDA advocated for regulations that would ensure the safety, effectiveness and reliability of drug products.²³⁴

During the eight months of the drug industry investigative hearings, from December of 1959 until September of 1960, the Subcommittee heard testimony from numerous scientists, drug industry associates, physicians, and academics. Early on the proceedings, the committee heard testimony from several pharmaceutical industry employees regarding the industry's practices, the salaries of its employees, and mechanisms of drug development. By the summer, the committee began hearing testimony from independent pharmacologists and physicians with experience performing tests and trials to develop drug products, including the head of the Department of Medicine at the University of Illinois, Chicago, Dr. Harry F. Dowling. The committee asked these medical professionals what they believed could be done to lower drug product prices.

Dowling's testimony was highly influential in the shaping of the proposed amendments. He advocated for the use of randomized, controlled, double-blinded clinical trials and disapproved of the influence of commercial practices on medical research. In 1959 Dowling stepped down from his posts on the editorial boards of the journals *Antibiotics and Chemotherapy* and *Antibiotic and Clinical Therapy* because

²³³ "Amendment of Antitrust Laws With Respect to Manufacture and Distribution of Drugs," Congressional Record – Senate, April 12, 1961, 5683, reprinted in "The Drug Amendments of 1962: Legislative History, Reports, Bills, Debate, Act," (Pharmaceutical Manufacturers Association, 1964).

²³⁴ Larrick, "Current Federal Drug Controls for Problems Old and New".

he believed that the quality of the journals had fallen due to the commercial interests of its editors and authors.²³⁵ Dowling testified in front of the Subcommittee in September of 1960 as an expert on infectious diseases, clinical pharmacology, and the medical uses of antibiotics. Kefauver immediately recognized Dowling's testimony as impressive and crucial to his goals of regulating drug pricing. Kefauver sent copies of Dowling's testimony to twenty-seven prominent physicians in the hopes of gaining support within the medical academic field for his committee's efforts to establish the need for new legislation.²³⁶

Dowling's testimony supported Kefauver's beliefs about drug regulation. Dowling advocated increasing the budget of the FDA, improving the federal facilities for testing drugs, compelling drug firms to use generic names on drug labels, tightening the regulations on drug advertisements and drug patents, and mandating that drug firms provide proof of efficacy and safety in NDAs.²³⁷ Dowling stated:

It should be obvious to everyone that insufficient knowledge on the part of the doctor regarding the efficacy of a drug can [be] to the detriment of a patient just as such as a toxic action by the drug, which the FDA now has the power to regulate.

Although the FDA Bureau of Medicine had long ago called for the regulation of drug efficacy, Dowling was among the first to testify in favor of empowering the FDA to determine the efficacy as well as the safety of drug products. Kefauver valued Dowling's testimony so highly because Dowling was an expert in the field of

²³⁵ Letter to Estes Kefauver from Harry Dowling, May 18, 1960, Dowling Papers, NLM, B10 F "Kefauver Legislation".

²³⁶ Letter to Harry Dowling from Estes Kefauver, September 26, 1960, Dowling Papers, NLM, B10 F "Kefauver Legislation".

²³⁷ Harry Dowling, "Statement Before Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, of the U.S. Senate," September 14, 1960, Dowling Papers, NLM, B10 F "Kefauver Legislation".

performing clinical trials on drug products for both academic facilities and commercial drug firms. Dowling noted the need for regulating the pharmaceutical industry without “[going] too far,” and diminishing its ability to develop new drug products. Dowling connected the high prices of the drug industry with the need to increase regulations on how companies developed drug products. He believed that for each new drug a company should obtain all possible facts about the compound, eliminate all false and misleading information, and increase the availability of valid information. Although Dowling’s testimony did not have any immediate impact on the American public, Kefauver believed that he convinced Congressmen and fellow testifiers of the validity of his convictions.

Kefauver’s aspirations to reduce the prices of drug ultimately aligned with the FDA’s desire for stronger regulations on the development of drug products. Upon the introduction of the first bill that resulted from the Subcommittee’s investigation, Kefauver stated:

If Congress is to accomplish anything of substantial benefit to our sick and afflicted people in the cost of medicine, we must pass new legislation. There appear to be two alternatives – price control or providing for freer competition. We are opposed to price control. The better course is to make more effective the operation of our traditional free enterprise system.²³⁸

Kefauver did not want to pass legislation that would over-regulate the drug industry, but he did want to pass legislation that would encourage fair competition between drug manufacturers. For example, he wanted to restrict the use of patents for drug products and compel all firms to label drug products with generic names. Beginning

²³⁸ “Sen. Kefauver and Rep. Cellar Introduce Legislation to Lower Drug Prices, Improve Protection,” Press Release from the Office of Estes Kefauver, April 12, 1961, Dowling Papers, NLM, B10 F “Kefauver Legislation”.

in the early twentieth century, numerous firms produced the same drug compounds under different brand names. Instead of promoting the generic or chemical name of the product, firms advertised their products using brand names, prompting consumers to believe in the superiority of specific brands. Kefauver proposed to increase competition in the drug industry by passing regulations that would assure physicians of the quality of all drug products, and especially of the quality of generic products.²³⁹ This included amending the sections of the FDCA concerning the acceptance of new drug products and manufacturing inspections.

Amending the FDCA to Lower Drug Prices: Legislative History

On April 12, 1961 Senator Kefauver and Representative Emmanuel Celler of New York introduced identical bills to their respective houses of Congress. Celler was the Chairman of the House Judiciary Committee and of its Antitrust Subcommittee. In a joint statement released to the press, Kefauver and Celler announced that they had written the bill in response to the questionable commercial practices of the drug industry. Kefauver's bill, S.1552, received the more attention than did the House bill. Kefauver's bill aimed to increase competition within the drug industry by requiring the licensure of all drug companies, enabling the FDA to be more selective in approving new drug products, and standardizing drug products with generic names. The passage of this initial bill would have amended the Sherman Anti-Trust Act, Patent Laws, and the FDCA. Specifically, the bill would have implemented several new requirements of the pharmaceutical industry including the federal licensure of all drug manufacturers and NDA applicants by the Department of Health,

²³⁹ "Amendment of Antitrust Laws With Respect to Manufacture and Distribution of Drugs". Dowling Papers, NLM, B10 F "Kefauver Legislation".

Education and Welfare, proof of efficacy for all new drug products, the use of generic names on all drug labels, and the inclusion of more information about drug efficacy and risks in product packaging. The AMA strongly opposed the inclusion of the efficacy requirement. AMA leaders believed that the Association should hold authority over deciding drug effectiveness.²⁴⁰

In order for the Senate to vote on the bill, both the Antitrust Subcommittee and the Senate Judiciary Committee would first have to accept the bill, which did not happen in 1961. The bill would have eliminated the possibility of patent agreements between companies and increased the stringency of manufacturing inspections. The patent provisions of the bill worried pharmaceutical companies executives more so than any other section of S. 1552. The bill would have decreased the viability of drug patents from seventeen years to three years for companies willing to pay the pioneer firm a small royalty. The bill also would have eliminated patent protections for ‘me-too’ drugs, also known as molecular alterations, and would have allowed the FDA claim the equivalence of generic drug products and their brand name counterparts. The Senate Antitrust Subcommittee heard testimony for and against the Kefauver’s bill from July of 1961 until the spring of 1962. The pharmaceutical drug industry, under the Pharmaceutical Manufacturers’ Association, and the AMA strongly opposed S. 1552. The opinions of the AMA and the PMA led Republican Senators Everett Dirksen and Illinois and Roman Hruska of Nebraska to prevent the acceptance of S. 1552 by the Senate Judiciary Committee.

²⁴⁰ American Medical Association, *Digest of Official Actions*, 196-197.

By the end of 1961, the opponents of the bill appeared to have ended Kefauver's attempts to pass S. 1552. Earlier in this chapter I quoted an anonymous pharmaceutical company medical director who criticized drug companies' sale of their failures. While this former industry employee spoke out against the drug industry, dozens of other drug company executives spoke out against Kefauver's bill. Opponents of the bill claimed that the bill would over-regulate the industry, diminish its production of new drug products, and intrude on the free-market system.²⁴¹ Supporters of the bill claimed that the bill would ensure the safety and health of the American people more thoroughly than the current drug industry regulations. In March of 1962 Kefauver rewrote large portions of S. and resubmitted it to the Subcommittee.

In the debates concerning S.1552, the participants spoke of the bill as regulating the pharmaceutical industry, rather than the drug products themselves. This represents a notable change from the debates surrounding the passage of the 1906 and the 1938 Acts, when legislators spoke about regulating drug products directly. By the 1950s, the pharmaceutical industry had become a cohesive industry to be regulated as a whole, unlike the fragmented drug industry of the first five decades of the century. Even though unconventional firms continued to produce drug products like Krebiozen, the public's understanding of the production and use of drug products became uniform. The American people came to embrace the idea that legitimate physicians prescribe only drug products developed and manufactured by

²⁴¹ "Odds Against Kefauver in Drug Industry Fight," *The Hartford Courant* (1923-1986), July 23, 1961, 7A; Jerry Landauer, "Vannevar Bush Hits Kefauver Drug Plan," *The Washington Post*, December 9, 1961; "Drug Industry Hits 3-Year Patent Bill," *New York Times*, July 27, 1961.

pharmaceutical companies. These companies used standardized scientific principles, including chemical analyses, animal testing, and controlled clinical trials to produce drug products.

By early 1962, Kefauver recognized that the passage of S. 1552 had stagnated in the Senate. He and his staff rewrote the bill in March of 1962 to accommodate many of the critiques the bill had received in the last several months, but the main tenets of the bill remained the same. On March 8, 1962 the Subcommittee accepted the amended S. 1552. Several days later, Senators Dirksen and Eastland of the Judiciary Committee suggested that the Subcommittee on Patents and Trademarks consider the bill. This committee removed the antitrust and compulsory licensing sections from S. 1552. Meanwhile, President Kennedy finally announced his support of the bill after remaining mostly silent on the issue since his inauguration. Kennedy wrote to Eastland, urging the enactment of S. 1552 with several of his own amendments.²⁴²

By June of 1962, Dirksen had submitted a revised copy of Kefauver's bill, known as the Eastland-Dirksen Bill. Dirksen's bill maintained that all firms had to prove the effectiveness of new drug products, but allowed firms to market drug products effective against one disease as effective against other diseases. The Dirksen bill did not require the certification of drug manufacturers or of antibiotic agents. Dirksen's bill, while still called S. 1552, retained very little of the bill Kefauver proposed in April of 1961. The Judiciary Committee accepted the weakened S. 1552

²⁴² Letter to James O. Eastland from John F. Kennedy, April 10, 1962, in Senate Report No. 1744, Drug Industry Act of 1962, July 19, 1962, reprinted in "The Drug Amendments of 1962: Legislative History, Reports, Bills, Debate, Act," (Pharmaceutical Manufacturers Association, 1964).

on July 12, 1962, but the bill was not discussed by the Senate because of great opposition by a number of Senators.

The FDA remained vocal about the proposed amendments throughout this process. In April of 1962, the FDA approached Representative Oren Harris with a bill authored by the Administration. The FDA removed the clauses regulating patents from the bill introduced by Kefauver and Celler in April of 1962, but retained the rest of the bill. The House Interstate and Foreign Commerce Committee continued to hear testimony on the Celler bill in spring of 1962 and began hearing testimony on the Harris bill in June. The FDA testified that the Dirksen bill would not be helpful to their regulation of drug products. By July of 1962, neither the House nor the Senate appeared close to passing a bill that would regulate the pharmaceutical industry.

Ultimately, the American media's portrayal of the thalidomide events encouraged Congress to pass a bill amending the FDCA in 1962. In April of 1962, the print media reported on the thousands of children born with phocomelia outside the United States.²⁴³ In the same month, pediatric researcher Dr. Helen Taussig testified at the Senate Judiciary Meeting on S. 1552. Dr. Taussig explained the events surrounding the use thalidomide and its toxicity. The media did not publicize Taussig's testimony in April, but they would propagate her ideas later in the summer. She stated:

Our food and drug laws are a great protection to our country. Nevertheless had this drug [thalidomide] been invented in this country, I believe it would have passed our present laws, as it is only under special circumstances that tests of pregnant animals are requested. The

²⁴³ Carpenter, *Reputation and Power*, 241.

recent disaster in Germany and England clearly indicates the necessity for stricter laws as regards to tests for safety and efficacy.²⁴⁴

In her testimony, Taussig displayed how the thalidomide story would be used to ensure the passage of the amendments through Congress in 1962. Taussig prompted Congressmen to fear the possibility of having a child born with terrible birth defects because of weaknesses in federal drug regulations. In July of 1962, the national media further emphasized this possibility for the American public. In his front page *Washington Post* article, Morton Mintz championed Dr. Kelsey as a true heroine who had saved America from a “bad drug.”²⁴⁵ The national media picked up the thalidomide story immediately after opponents to the Kefauver amendments had weakened the House and Senate bills to amend the FDCA. An article in the *Chicago Daily News* claimed that Kefauver encouraged Mintz to publish the story.²⁴⁶ At this point, no one had introduced a bill into the Senate or the House that increased the regulations on investigational drugs. On July 31, Kefauver announced that he recommended an amendment to S. 1552 that would require adequate animal testing on new drug products.²⁴⁷

The country’s admiration for Frances Kelsey also sparked public interest in promoting amendments to the FDCA that she supported. Over the summer of 1962, the content of the proposed amendments shifted from emphasizing regulations on the commercial practices of the pharmaceutical industry to regulations on their methods

²⁴⁴ “Statement of Dr. Helen Taussig on H.R. 6245,” Kelsey Papers, LOC, B34 F2.

²⁴⁵ Mintz, “Heroine of the FDA Keeps Bad Drug Off of Market.”

²⁴⁶ James McCartney, “How Drug Lobbyists Lost Big Battle,” *Chicago Daily News* October 16, 1962.

²⁴⁷ “Sen. Kefauver Recommends New Drug Amendment as Result of Disastrous Case of Thalidomide,” Press Release July 31, 1962, from the Office of Sen. Estes Kefauver, Frances O. Kelsey Papers, LOC, B34 F2.

of drug development. On August 7, President Kennedy awarded Kelsey a President's Award for Distinguished Federal Civilian Service. The ceremony followed Kennedy's announcement that the Dirksen bill S. 1552 would not sufficiently protect the consumer; he urged the passage of the Harris bill, authored by the FDA. Soon after, the President's staff wrote a bill combining the Harris bill with the original Kefauver bill to create a bill much like the original S. 1552 with minimal patent restrictions. The bill removed the automatic approval provision of the FDCA, allowed for the removal of approved drug products from the market, required firms to distribute truthful package inserts, required firms to report drug side effects, and mandated that HEW would review all generic names. The President requested that the Senate Judiciary Committee accept this bill, and they did so on August 20, 1962. When the Senate took up the bill, Kefauver proposed an amendment to this bill that would require firms to perform animal testing on drugs "before a new drug may be distributed by a manufacturer to scientific experts for testing and evaluation of its effects in human beings."²⁴⁸ The Senate unanimously accepted Kefauver's amendment. Senator Jacobs also proposed an amendment that would require physicians to obtain a patient's permission before treating patients with experimental drug products. Most Senators initially opposed this amendment. However, HEW soon issued a press release announcing that some patients may have taken thalidomide unknowingly and warning that pills given to patients in unmarked containers could contain thalidomide. This drastically increased public support for increased

²⁴⁸ Estes Kefauver, "In the Senate of the United States, Amendment to S. 1552," Kelsey Papers, LOC, B34 F2.

regulations on drug development. The Senate approved the amended President's bill unanimously, with Jacobs and Kefauver's amendments.

The House continued to hear testimony on the Harris Bill in September and members proposed numerous unsuccessful amendments to weaken the bill. The House accepted the bill by the end of September. Opponents to the original bill had removed the requirement of animal testing and the requirement of distributing package inserts to physicians, and weakened the regulations on advertising. On October 1, members of the House and Senate Judiciary Committees met to create a single bill to be approved by houses. Kefauver successfully included a number of the provisions that had been dropped by both the House and the Senate. On October 3, the Senate approved the bill and on October 10, 1962 President Kennedy signed the Drug Amendments into law.

*The 1962 Drug Amendments and the 1963 Investigational Drug Regulations*²⁴⁹

The heading to the 1962 Drug Amendments states that the Congress intended to “protect the public by amending the Federal Food, Drug and Cosmetic Act to assure the safety, effectiveness, and reliability of drug products, authorize standardization of drug names, and clarify and strengthen existing inspection authority.”²⁵⁰ These regulations represent the longest and most extensive changes Congress had made to the FDCA since 1938. The amendments dealt with the three main issues named in the heading. Ironically, the law did not affect the patenting of drug products, even though Kefauver initially began investigating the drug industry to

²⁴⁹ This section outlines the content of the 1962 Drug Amendments from my own reading of the text.

²⁵⁰ *The Drug Amendments of 1962*. Public Law 781, *U.S. Statutes at Large* 76 (1962): 780-796.

limit their profits from patented products. The amendments focused mostly on regulating the sale and investigational use of drug products. The amendments did not change the patenting rights companies held on drug products after they had introduced them into the market.

Congress required firms to prove both safety and efficacy in NDAs and allowed HEW to refuse and suspend NDAs of drug products found to be unsafe or unreliable by new data. As requested by President Kennedy, the law required firms selling drug products already approved by the FDA to maintain records on the reported side effects of these products and to allow HEW access to these records. The new law required firms to submit reports on animal testing and other pharmacological experiments “adequate to justify the proposed clinical testing” before legally beginning clinical trials. Under this clause, the FDA established the Investigational New Drug Application (IND) for firms to submit before beginning clinical trials. The law also required physicians and investigators to inform patients that they would be given investigational drugs before administering such drugs.²⁵¹ Finally, the law allowed HEW 180 days to review NDAs (increased from sixty days), which gave the agency greater ability to thoroughly analyze the firm’s application.

The amendment provided for the establishment of certification for all antibiotics. It also allowed HEW to designate official names for all drug compounds “identical in chemical structure and pharmacologic action,” which we now

²⁵¹ This clause represents the first instance of regulations on the ethics of clinical trials and their use of human subjects. In the 1960s, the government instigated more thorough regulations on this subject.

understand to be generic names.²⁵² The amended law required all facilities involved in the “manufacturing, preparation, propagation, compounding, or processing” of drug products with the federal government to register with the government and clarified that inspections of food, drug, and cosmetic manufacturing facilities could not include the inspection of pricing and sales information. HEW also gained authority over prescription drug advertising. The law specified that drug product advertisements must be true, use official (generic) names along with brand names, and include side effects and effectiveness information. Congress gave HEW this authority, previously held by the FTC, without any serious dispute, even though it had caused such controversy in the 1930s.

While Congress debated the final provisions of S. 1552 and the Harris bill, the Department of Health, Education and Welfare worked directly with the Bureau of Medicine to produce a set of regulations for investigational drugs. The Medical Director of the Bureau of Medicine, Julius Hauser initially wrote the IND rules in May of 1962, when he would have been aware of the effects of thalidomide, as Merrell had withdrawn the Kevadon NDA in March.²⁵³ He and his staff revised the rules into an application for firms to submit before beginning clinical trials on new drug products during the summer. HEW published the form for accepting “New Drug for Investigational Use” in the *Federal Register* on August 10, 1962.²⁵⁴ This proposed change to the CFR would codify how the FDA required firms to perform

²⁵² *The Drug Amendments of 1962*. Public Law 781, *U.S. Statutes at Large* 76 (1962): 789-790.

²⁵³ Carpenter, *Reputation and Power* 276 n.72.

²⁵⁴ Department of Health, Education and Welfare, Food and Drug Administration, Press Release August 9, 1962, NSMR Papers, NLM, B24 “Federal Legislation 1”.

initial experiments, animal testing, and clinical trials while developing drug products. The stipulations of the Drug Amendments passed in October strengthened the authority of the new form for investigational drugs because the law gave the FDA authority over the investigation of unapproved drug products. The IND Application required firms to submit data from adequate chemical analysis and animal testing to ensure the safety of the drug, a complete plan of the proposed clinical trials, and credentials of the proposed investigators. HEW also required that the firms keep records of ongoing clinical trials that included the side effects of the drugs, results, and case studies of the individual participants.

After HEW published the IND in the *Federal Register*, they received comments from the industry and other researchers complaining that the new form was too strict and formalized and would impede drug development research. HEW responded by clarifying how much information they required from each stage of the clinical investigations. In January of 1963, HEW released a new draft of the IND that differentiated between three stages of clinical trials. During stage one and stage two trials, firms would perform clinical pharmacology assessments. This included initial safety testing in humans with only a small number of participants; the IND required minimal information about these trials. During the first stages the FDA wanted firms to take as many precautions as possible to ensure the safety of the participants. The third stage of investigation was the clinical trial, performed on a large scale at multiple locations. The application required more information on planning of the full clinical trial, but also allowed for some variation between the planned trial and the performance of the trial. In allowing for variance, HEW hoped to diminish drug

companies' fears that the rules would constrain the drug development process. The new form also allowed firms to submit "adequate" records instead of "complete" records.

The FDA adopted the Investigational New Drug Application on February 7, 1963 and finalized the rules in August of 1963.²⁵⁵ As of that point, HEW required firms to submit an IND before performing clinical trials. The FDA could terminate clinical trials organized by a firm that did not submit an IND or that did not keep up with regulations. However, the 1963 Investigational Drug Regulations did not require the approval of the IND before firms could begin clinical testing. The rules only allowed the FDA to stop a trial after it had been commenced.

In August of 1963, HEW named Frances Kelsey as the head of the new Investigational Drug Branch of the FDA's Division of New Drugs.²⁵⁶ Kelsey controlled the enforcement of the IND Rules and elaborated on the practical use of the rules. Kelsey gave numerous speeches on the new regulations of investigational drugs in 1963 and 1964 that specified how the Administration would enforce the new rules.²⁵⁷ By July of 1964, Kelsey and her staff had terminated only nine trials out of almost two thousand IND forms submitted by drug companies.²⁵⁸ In December of

²⁵⁵ Department of Health, Education and Welfare, Food and Drug Administration, Press Release January 6, 1963, NSMR Papers, NLM, B24 "Federal Legislation 2"; Carpenter, *Reputation and Power*, 275.

²⁵⁶ Bridget M. Kuehn, "Frances Kelsey Honored for FDA Legacy," *Journal of the American Medical Association* 304, no. 19 (2010): 2109-2112.

²⁵⁷ Some speeches include, "Clinical Regulations" February 1963, "Investigational Drug Branch: Objectives and Functions," June 1963, "New Drug Laws in Action" November 1963, "Use of Investigational Drugs in Hospitals," June 1964, Kelsey Papers, LOC, B20 F11.

²⁵⁸ Carpenter, *Reputation and Power*, 286. Carpenter attributes this low number both to Kelsey's small staff and to the adherence of firms and researchers to the new rules.

1963, the Branch rejected the IND form for Krebiozen, halting Research Laboratories' clinical experimentation. In January of 1963, the FDA had sent a letter to Durovic and Ivy informing them of the need to submit a plan for further clinical investigation under the new Kefauver-Harris amendments.²⁵⁹ Durovic and Ivy submitted an IND form by June of 1963, but the Administration did not believe the plans met legal requirements. The FDA terminated the ongoing investigational studies of Krebiozen that year; however, Durovic and Ivy continued to distribute the drug.²⁶⁰ The government brought Durovic and Ivy up on charges for introducing a mislabeled drug product into interstate commerce in October of 1963. Much like the cases against the Hoxsey and Koch Cancer Cures, the jury could not reach a verdict. However, the FDA could now continue to prevent the firm from distributing the drug for investigational use.

Conclusion

In 1968 Morris Fishbein, editor of *Medical World News* and former editor of *JAMA*, stated, "Laws are passed for the times in which they occur... The bills are not written, they are rewritten and amended."²⁶¹ Fishbein believed that Congress would have passed the Kefauver amendments without the thalidomide scandal, but that the bill would have been different. Winton Rankin, a member of FDA Commissioner George Larrick's staff, stated that the efficacy provision of the amendments would

²⁵⁹ Letter to Drs. Stevan Durovic and A. C. Ivy from Boisfeuillet Jones, January 31, 1963, Kelsey Papers, NLM, B20 F7.

²⁶⁰ Department of Health, Education and Welfare, Office of the Secretary, "Press Release June 7, 1963," Kelsey Papers, NLM, B20 F7.

²⁶¹ Fishbein, *The History of the AMA*, 101-102.

not have been included without the thalidomide events. I argue that the thalidomide events affected both the passage and the content of the 1962 Drug Regulations.

Specifically, the thalidomide story prompted Kefauver to include a clause in the amendments requiring firms to perform animal testing before performing clinical trials by demonstrating the potential hazards of investigational drugs. Thalidomide also prompted Senator Jacobs to propose an amendment requiring the organizers of clinical trials to notify patients if they gave them unapproved, investigational drugs. This short clause foreshadowed the passage of a series of regulations on informed consent and the ethics of clinical trials in the late 1960s and 1970s. The thalidomide events also encouraged President Kennedy to become involved in the passage of S. 1552 because of the media's attention to the issue. As Fishbein and Rankin claimed, Congress probably would have passed some form of S. 1552 in 1963 or 1964 without the discovery that thalidomide caused birth defects. However, thalidomide both expedited the passage of new drug regulations and shaped the content of these regulations.

While the success of penicillin prompted pharmaceutical companies to produce more drug products (especially antibiotics) using pharmacological methods and hastened the expansion of the drug industry, the failure of thalidomide prompted the government to regulate this newly established industry. The thalidomide events directly motivated Congress to propose amendments requiring physicians to inform patients when they received investigational drugs and requiring firms to report all observed side effects of drugs and to perform animal testing before beginning clinical trials. The concept of separating clinical research on drugs into distinct phases did not

arise until the fall of 1962 in discussions within the Bureau of Medicine.²⁶² The Bureau reached this conclusion not because of any one drug, but because of the need to codify the professionally and academically accepted performance of clinical trials.

The makers of Krebiozen demonstrated to the FDA that the lack of regulations on investigational drugs allowed firms to continue to distribute drug products despite the FDA's opposition. The popularity of Krebiozen into the late 1950s and early 1960s prompted Frances Kelsey and other members of the Bureau to consider implementing precise regulations asserting the legal methods of developing drug products. The FDA learned that not all physicians and researchers would accept the FDA's classification of a therapeutic product. That is, some physicians would not discard a drug simply because the FDA rejected it.

The Kefauver-Harris Amendments gave the FDA the authority to require preclinical testing, animal studies, and three phases of clinical trials of all firms investigating new drugs. Many of the amendments of the Kefauver-Harris Act were not novel concepts. The FDA, medical researchers, and pharmaceutical firms all employed clinical pharmacology methods from the late 1940s. Overall, the final Drug Amendments aligned with the FDA's desires for new provisions, including the desire of administrators to distance the administration from regulating drug prices.²⁶³ The FDA would have preferred tighter controls on non-prescription drug products, but

²⁶² Carpenter, *Reputation and Power*, 278.

²⁶³ Rankin, 101-102; Carpenter, *Reputation and Power*, 194.

Kefauver decided to restrict most of the bill to prescription drug regulation to avoid political opposition from the proprietary medicine industry.²⁶⁴

Kevadon and Krebiozen represent two very different types of drug products from the 1950s. Krebiozen was an ineffective treatment for a serious, chronic disorder. Thalidomide was an effective but unsafe sedative drug. The experience of FDA administrators with Krebiozen encouraged them to implement rules systematizing the development of new products. The experience of FDA administrators with Kevadon prompted legislators to amend federal laws regulating the development and labeling of new drug products. In the 1950s, the pharmaceutical industry became a commercial, profitable industry that sold scientifically developed products. On a conceptual level, Congress reacted to the new industry by implementing regulations that controlled both the sale of drug products, in 1951, and the scientific development of drug products, in 1962.

²⁶⁴ Rankin, 101. By the early 1960s, the proprietary medicine industry produced mostly over the counter drugs. The differentiation between the ethical drug industry and the proprietary drug industry had been codified by difference in their methods of use by conventional physicians.

Conclusion: The Historical Context of the Contemporary System of Drug Regulation

In starting this project, I aimed to create an account of legislative change over time informed by the history of American medicine. Developments in chemistry, biology, physiology, pharmacology, and other medical research fields changed the products of the drug market over the course of the twentieth century. In turn, these products influenced how the public and legislators believed the government should regulate the development, manufacture, sale, and use of these products. As discussed, the introduction and commercial success of especially novel drug products directly impacted the crafting and passage of federal regulations by changing the way in which Americans defined drug products. It was this novelty that shaped how Congressmen constructed new regulations. The commercial success and public response to these products encouraged legislators to consider implementing new regulations initially and ensured the passage of these regulations.

Throughout the first six decades of the twentieth century, Congress passed legislation responding to current products of the drug industry, rather than those they believed would be sold in the future. In 1938 the sulfonamide products, the first class of scientifically developed drug products, convinced Congress to regulate these products using scientific standards and methods to ensure the safety of drug products. During the 1940s, penicillin and streptomycin emerged as the first effective drug cures. Congress responded to their widespread use in America by implementing regulations to ensure that firms manufactured these products consistently and that public used these products under the supervision of medical professionals (when the

FDA deemed necessary). Without the investigational use of Krebiozen and Kevadon in America, Congress may not have perceived that clinical trials on unsafe and ineffective drugs could be detrimental to the public health.

I have repeatedly stressed the importance of commercial success for the products that prompted changes in drug regulations. The commercial success of these products, in addition to their originality, meant that legislators, physicians, and the public knew about them and subsequently considered their use as having a significant influence on the health of the American people. The public reception of these products, including their support for the sulfa drugs, penicillin, and Krebiozen, and their horror at the potential dangers of the Elixir Sulfanilamide and Kevadon, expedited the legislative process and ensured the passage of new drug regulations.

While the national media played a role in the passage of several drug regulatory laws, their coverage of scandals in the drug industry did not determine the content of these regulations. Congress passed the three major pieces of legislation that I discussed in the aftermath of the national media's coverage of the faults of the drug industry. The passage of the 1906 Act followed immediately after several muckrakers picked up stories about the dangerous chemicals in many food and drug products. The media paid substantial attention to the deaths that resulted from the Elixir Sulfanilamide and to the birth defects in the children of mothers who had taken thalidomide products. In each of these cases, however, Congress had begun discussing bills proposed to regulate the drug industry for several years before the media picked up these sensational stories. While the Elixir and Kevadon both caused legislators to add new clauses into the bills they had already introduced, other

products, like the sulfanilamide products sold by ethical drug firms and Krebiozen, prompted FDA officials, and eventually legislators, to consider these regulations initially. Both drug products that gained national attention for negative reasons and those that had a significant impact on the American public for their effectiveness shaped legislative change to federal drug regulations.

Today, the FDA continues to regulate drug production through the use of two approval processes: one for firms to begin performing clinical trials with drugs, and one for firms to begin selling drug products. In establishing this system, which has been in place for fifty years, Congress aimed to increase the extent to which drug products remedied public ailments, and to decrease the risks of drug production process caused for Americans. I must point out again that the regulations discussed had a significant impact on the majority of drug products on the American market. My argument rests on products that stood out from the market as unique in either their method of development, therapeutic effectiveness, extreme dangerousness, or potential for harm.

This thesis focuses on a specific series of drug regulations because they represent those that formed the pre-market approval system used to regulate the drug industry today. However, a much more detailed study could have been done on any of the regulations I discussed. In addition, this thesis directly encourages further study on the federal regulations and codifications concerning the use of human subjects in clinical trials in the 1960s and 1970s and on the Animal Drug Amendments of 1968, both of which confronted issues of bioethics, a field that studies the ethical questions

generated by biology and medicine that I have not discussed.²⁶⁵ This thesis also prompts questions about how the regulations themselves impacted the products of the drug industry in the United States. Another study could explore the way in which the pharmaceutical industry reacted to new regulations and the consequences of these regulations for the public health.

*

In retrospect, we know that the novel products discussed in this thesis foreshadowed future products of the pharmaceutical industry. Antibiotics, cancer chemotherapeutics, and lifestyle drug products all became produced commonly in the United States. Despite this, I still claim that Congress enacted federal drug regulations in reaction to products of the contemporaneous market, rather than those of the market they envisioned in the future. For this reason, drug regulatory laws in the United States are unique to products that have been distributed and sold in America and how the public has responded to these products, both in their actual usage and in their perceptions of them. Congress did not construct the American drug regulatory system on the concept of an idealized system of “magic bullets” or consistently ethical drug manufacturers. In this sense, the establishment of this particular system was not inevitable in a society in which drug products were a part of the commercial market. Perhaps, however, the establishment of a system reacting to contemporaneous products was inevitable, given the American democratic system and use of bureaucratic bodies.

²⁶⁵ Jill Fisher, *Medical Research for Hire*, (New Brunswick, NJ: Rutgers University Press, 2009), 221 n9.

Appendix A

Documents included in a New Drug Application as mandated by the 1938 Federal Food, Drug and Cosmetic Act (Public Law 717, Sec 505 (b))

- (1) Full reports of investigations which have been made to show whether or not such drug is safe for use
- (2) A full list of the articles used as components of such drug
- (3) A full statement of the composition of such drug
- (4) A full description of the methods used in and the facilities and controls used for, the manufacture, processing and packing of such drug
- (5) Such samples of such drug.

Appendix B

List of Acronyms

FDA: Food and Drug Administration

USP: United States Pharmacopeia

NF: National Formulary

NNR: New and Nonofficial Remedies

USDA: United States Department of Agriculture

PHS: Public Health Service

FTC: Federal Trade Commission

BOC: Bureau of Chemistry, USDA

AMA: American Medical Association

APhA: American Pharmaceutical Association

FDCA: Federal Food, Drug and Cosmetic Act of 1938

FSA: Federal Security Agency

HEW: Department of Health, Education and Welfare

HHS: Department of Health and Human Services

OSRD: Office of Scientific Research and Development (WWII)

CMR: Committee on Medical Research (WWII)

CCOA: Committee on Chemotherapeutic and Other Agents (WWII)

NRRL: Northern Regional Research Alliance Laboratories, USDA

FSA: Federal Security Agency

NDA: New Drug Application

IND: Investigational Drug Application

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