

6-9-2014

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### Recommended Citation

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Available at: <https://archives.law.nccu.edu/siplr/vol7/iss1/2>

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# THE ROLE AND MISSION OF THE UNITED STATES FOOD AND DRUG ADMINISTRATION: REGULATOR, WATCHDOG, FACILITATOR OR “ALL OF THE ABOVE”

*Roseann B. Termini, Esq.*  
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## Introduction

What would transpire if the United States Federal Food and Drug Administration (FDA) did not exist? The charge of this inquiry is to analyze whether or not pharmaceutical companies by way of illustration would comply with the Federal Food, Drug and Cosmetic Act if this administrative agency did not exist. The mission of the FDA is the promotion of public health through prompt and efficient review of clinical research and the taking of appropriate action on the marketing of regulated products in a timely manner.<sup>1</sup> Is the FDA a regulating agency? Is the FDA a watchdog agency? Is the FDA a facilitating agency? The simplest and most obvious answer is that the FDA functions as all three. The relationship between the multi-functional role of the FDA and the question of whether or not drug companies would comply if the agency did not exist provides the basis for this article.

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\* The authors wish to thank the NCCU Biotechnology and Pharmaceutical Law Review editors and in particular Ms. K. Andrews, articles editor for the excellent editorial recommendations.

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1. 21 U.S.C. § 393 (2012).

First, the expanse of FDA regulation is all encompassing. That is, FDA regulatory authority extends to several types of products such as foods, human and veterinary drugs, medical devices, cosmetics, dietary supplements, biologics, and tobacco. However, this article will focus on pharmaceutical regulation to serve as an illustration of the interplay between FDA and the regulated industry. A historical overview will provide the origin to explain the need, foundation, and development of regulation geared towards drug law regulation as it exists in the United States today. Second, the FDA will be analyzed into its functions as regulator, watchdog and facilitator. Each of the three sections will address the ultimate question posed and draw conclusions as to whether the pharmaceutical industry could or would self-regulate so as to comply with Congressional mandates in the absence of the FDA.

Yet, a simple yes or no answer could not possibly suffice in formulating the ultimate determination. However, a look back at history, case law, and the expansive reach of the FDA strongly suggests that while many, if not most drug companies, would comply or attempt to comply with federal law, a climate without a strong administrative agency to oversee the pharmaceutical industry would simply be too precarious to the public health to justify.

## **PART I: A Look Back at the Past Unravels the Current Regulatory Atmosphere**

Determining whether or not pharmaceutical companies would comply with Congressional mandates requires an understanding of why Congress was compelled to establish a regulatory agency aimed at the drug industry. History provides the starting point for discussion. This section discusses not only when and why the federal government established a drug regulatory agency, but will highlight why, how and at what points Congress and the judicial system broadened the scope and ultimately the regulatory power of what we know today as the Food and Drug Administration.

### **The 1906 Pure Foods and Drug Act and *United States v. Johnson*- Impetus for the Sherley Amendment**

The Food and Drug Administration is the oldest comprehensive consumer protection agency in the United States federal govern-

ment.<sup>2</sup> The earliest evidence of federal intervention concerning food and drug regulation was the appointment of Lewis Caleb of the United States Patent Office around 1848 to conduct chemical analyses of agricultural products.<sup>3</sup> At the turn of the 20th century, Dr. Harvey Washington Wiley, Chief Chemist of the Bureau of Chemistry in the Department of Agriculture spearheaded an investigation into widespread adulteration of syrup in the United States marketplace.<sup>4</sup> At around the same time, author Upton Sinclair<sup>5</sup> drew public attention to the deplorable conditions in the United States meat packing industry with his novel, *The Jungle*. Pressure and public outrage over these circumstances as well as the determination of Dr. Wiley to provide consumer protection through federal regulatory intervention drove the passage of the Pure Food and Drugs Act of 1906.<sup>6</sup> The law prohibited the interstate transport of unlawful food and drugs under penalty of product seizure and/or criminal prosecution.<sup>7</sup>

While Dr. Wiley was more focused on chemical additives in foods, issues surrounding the potential mislabeling and advertising of drugs took center stage when the Supreme Court of the United States held in *United States v. Johnson* that false or misleading therapeutic claims as to remedial effects on drug labels are not “misbranding” within the meaning of the Food and Drugs Act of June 30, 1906.<sup>8</sup> The Court interpreted the statutory language to exclude therapeutic claims based upon the theory that the scope of ‘misbranding’ was limited to the ‘the identity of the article, possibly including its strength, quality, and purity.’<sup>9</sup>

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2. John P. Swann, *About FDA: History*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm> (last accessed July 1, 2012). See also, Roseann B. Termini, FOOD AND DRUG LAW FEDERAL REGULATION OF DRUGS, BIOLOGICS, MEDICAL DEVICES, FOODS, DIETARY SUPPLEMENTS, COSMETICS, VETERINARY AND TOBACCO PRODUCTS, at 2 (5th ed. 2012)

3. *Id.*

4. *Id.*

5. Upton Sinclair was a novelist and social crusader from California who pioneered what is called ‘muckraking journalism,’ which is reform-oriented, investigative reporting. ‘The Jungle’ was an expose on the substandard conditions in the meatpacking industry in the early 20th century. *Social Security History*, <http://www.ssa.gov/history/sinclair.html> (last accessed July 1, 2012).

6. Pure Food and Drug Act of 1906, 34 Stat. 768, 59 Cong. (1906) *repealed by* Act of June 25, 1938, 52 Stat. 1059 (1938).

7. *Id.*

8. *United States v. Johnson*, 221 U.S. 488 (1911).

9. *Id.* at 497.

### The Sherley Amendment Remedies False or Misleading Claims

In 1912, Congress reacted to *United States v. Johnson* by enacting the Sherley Amendment to the Pure Food and Drugs Act of 1906 (1906 Act).<sup>10</sup> The language of the statute was amended to explicitly state that false therapeutic claims are prohibited under the 1906 Act.<sup>11</sup> The amendment was not as effective as Congress would have hoped.<sup>12</sup> The elimination of the semantic loophole created in the original 1906 Act regarding false therapeutic claims exposed another difficult obstacle for the federal government; the burden of proving that the drug manufacturer was in fact attempting to defraud the public. While seizures of misbranded and adulterated drugs increased in the years following the enactment of the amendment, this obstacle proved extremely difficult in prosecuting cases under the amended Pure Food and Drugs Act.

### The Court in *United States v. Ninety-Five Barrels* Lifts the Intent to Defraud Burden

In 1924, the Supreme Court of the United States addressed this difficult burden on the government in *United States v. Ninety-Five Barrels*.<sup>13</sup> The Court held that the 1906 Act condemned every statement, design or device which may mislead or deceive, even if technically true.<sup>14</sup> The defendant sold apple cider vinegar labeled as follows; ‘apple cider vinegar made from selected apples’.<sup>15</sup> The cider, however, was made with evaporated apples, rather than unevaporated apples.<sup>16</sup> The cider was the expressed juice of apples and is so generally known and because it made no difference whether vinegar made from dried apples was not inferior to apple cider vinegar made with unevaporated apples, the Court found the label misleading and in vio-

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10. Sherley Amendment, 37 Stat. 416 (1912).

11. *Id.*

12. *Milestones in Food and Drug Law History*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm081229.htm> (last accessed July 1, 2012).

13. *United States v. Ninety-Five Barrels More or Less Alleged Apple Cider Vinegar*, 265 U.S. 438 (1924).

14. *Id.*

15. *Id.* at 444. See also, ROSEANN B. TERMINI, *FOOD AND DRUG LAW FEDERAL REGULATION OF DRUGS, BIOLOGICS, MEDICAL DEVICES, FOODS, DIETARY SUPPLEMENTS, COSMETICS, VETERINARY AND TOBACCO PRODUCTS*, at 2 (7th ed. 2014).

16. *Id.*

lation of federal law.<sup>17</sup> This decision began to erode the principle set forth in the Sherley Amendment that the government must establish the intent of the drug company to defraud the consumer. (This probably needs a cite—this is derived from some reading, so it is not common knowledge or an original thought).

### **The Elixir Sulfanilamide and the Evolution of the Food, Drug, and Cosmetic Act of 1938 (FDCA)**

In 1927, Congress formed the Food, Drug, and Insecticide Administration, and then, in 1930, changed the name to the Federal Food and Drug Administration.<sup>18</sup> The FDA was transferred from the Department of Agriculture to the Federal Security Agency (later known as the Department of Health, Education and Welfare) then to the Public Health Service, which is incorporated into the Department of Health and Human Services.<sup>19</sup> In 1933 the newly named agency recommended a complete overhaul of the 1906 Act as it was deemed obsolete against the atmosphere of both the food and drug industries. The FDA exemplified its contention that the 1906 Act was obsolete as it related to drug regulation by noting that several worthless and even life-threatening products would have been protected by the 1906 Act.<sup>20</sup> Among the items deemed critical for the law to address were the prohibition of false therapeutic claims for drugs, clarification of the right of the FDA to conduct factory inspections, control of product advertising, and premarket approval of all new drugs.<sup>21</sup> The Senate initiated the proposed legislation and it launched a five-year legislative battle.<sup>22</sup> The pending legislation stagnated in Congress for nearly five years until 1937, when a near public health disaster thrust what would eventually become the Food, Drug, and Cosmetic Act into action by Congress.<sup>23</sup>

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17. *Id.* at 444-45.

18. *Significant Dates in U.S. Food and Drug Law History*, <http://www.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm> (last accessed July 1, 2012).

19. John P. Swann, *FDA's Office History*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm> (last accessed on July 4, 2012).

20. Products implicated included Banbar, Lash-Lure, Radithor, and Wilhide Exhaler. John P. Swann, *About FDA: History*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054826.htm> (last accessed July 1, 2012).

21. *Id.*

22. *Id.*

23. 21 U.S.C. § 301 (1938).

In 1937, S. E. Massengill Co., a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glycol (DEG) as a solvent, and called the preparation “Elixir Sulfanilamide”.<sup>24</sup> The chief pharmacist and chemist of the company Harold Watkins, was not aware that DEG was poisonous to humans yet, at the time it was known in the industry.<sup>25</sup> The company marketed the product after adding a raspberry flavoring.<sup>26</sup> The elixir was meant to treat streptococcal infections; however, the untested, poisonous concoction ultimately caused the death of nearly 100 people, many of whom were children. (Cite) This incident and the subsequent public outcry propelled Congressional action to enact the Food, Drug and Cosmetic Act of 1938 (FDCA). Most notably was the requirement that manufacturers would now have to establish to the FDA that their drugs were safe *before* they could be sold to the public.<sup>27</sup> The FDCA not only provided public protections against potentially dangerous drugs, but also stimulated medical research and progress generally.

### **Warning Labels, Directions for Use, and the Prescription Requirement: The Durham-Humphrey Amendment of 1951**

The FDA quickly enforced the recently enacted FDCA by distinguishing over the counter drugs from drugs requiring prescription.<sup>28</sup> Prior to this amendment, all drugs were available for purchase over the counter without legal authorization from a health practitioner. The FDA created a class of drugs which could only be dispensed by prescription by a physician for stated uses.<sup>29</sup>

Much debate among the FDA, healthcare professionals, and the pharmaceutical industry followed regarding what constitutes an over the counter drug versus one that requires authorization from a healthcare professional. The Durham-Humphrey Amendment of 1951 ad-

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24. Steven Gilbert, *Elixir Sulfanilamide*, <http://toxipedia.org/display/toxipedia/Elixir+Sulfanilamide> (last accessed July 1, 2012).

25. *Id.*

26. *Id.* See also, ROSEANN B. TERMINI, FOOD AND DRUG LAW FEDERAL REGULATION OF DRUGS, BIOLOGICS, MEDICAL DEVICES, FOODS, DIETARY SUPPLEMENTS, COSMETICS, VETERINARY AND TOBACCO PRODUCTS, at 3 (5th ed. 2012).

27. 21 U.S.C. § 355 (2010).

28. 21 U.S.C. § 353(b).

29. *Id.*

dressed this issue.<sup>30</sup> Drugs that are potentially habit forming, toxic, or manifest potentially harmful effects demarcated those requiring a prescription from those available over the counter.<sup>31</sup> The Durham-Humphrey amendment mandated that the manufacturer provide adequate directions for use.<sup>32</sup>

### **Thalidomide and the Kefauver-Harris Drug Amendments of 1962**

Thalidomide, a drug developed in Germany, was dispensed as a painkiller and sleep aid.<sup>33</sup> The drug was approved by several Western European countries. Thalidomide was used along with dexamethasone to treat multiple myeloma in people who had been recently found to have this disease.<sup>34</sup> In the late 1950s and early 1960s thalidomide was prescribed to pregnant women in many countries to combat ‘morning sickness’. Unfortunately, the drug breached the placental barrier and caused damage to the developing fetus in multiple instances worldwide.

Due to the astute intervention of Frances Kathleen Oldham Kelsey, M.D. this tragedy was averted in the United States.<sup>35</sup> Dr. Kelsey was hired by the FDA in 1960 to review drug applications.<sup>36</sup> Pharmaceutical manufacturer Richardson Merrell applied to the FDA for thalidomide approval under the trade name Kevadon. Although thalidomide was approved in many countries, and despite pressure from the manufacturer, Dr. Kelsey withdrew her approval for the drug and insisted that it be fully tested prior to approval. Dr. Kelsey was subsequently honored for her heroism by then President John F. Kennedy.<sup>37</sup>

Having narrowly averted disaster with thalidomide, Congress took note of the questionable state of science in supporting drug ef-

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30. Durham-Humphrey Amendment of 1951, 21 USC 353 (1951).

31. *Id.*

32. *Id.*

33. *A Meta-analysis and Sytematic Review of Thalidomide for patients with previously untreated multiple myeloma*, <http://www.ncbi.nlm.nih.gov/pubmed/health/PMH0025700/> (last accessed July 1, 2012).

34. *Id.*

35. Wallace F. Janssen, *Frances Oldham Kelsey: Medical reviewer famous for averting a public health tragedy*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/ucm345094.htm>.

36. *Id.*

37. *Id.*

fectiveness and the claims made in labeling and advertising by passing the Kefauver-Harris Drug Amendments of 1962.<sup>38</sup> Before marketing a drug, pharmaceutical manufacturers now had to prove safety as well as provide substantial evidence of effectiveness for the intended use of the product.<sup>39</sup> In order to prove that effectiveness, firms were now required to provide evidence through well-controlled studies.<sup>40</sup> Corollary to this requirement was the requirement of informed consent of study subjects.<sup>41</sup> The 1962 amendments also required that the FDA specifically approve the marketing application before the drug could be marketed.<sup>42</sup> All of these marked major changes for the pharmaceutical industry as Congress increasingly expanded the regulatory power of the FDA.

### **1970s *Upjohn v. Finch* and the Standard of Substantial Evidence as to Drug Efficacy, Patient Inserts and Over-the-Counter Products**

In 1956 the Commissioner of the FDA promulgated regulations providing that certain antibiotic drugs could be certified as safe and effective.<sup>43</sup> The Upjohn Company manufactured one such product, called Panalba, which was approved and certified by the FDA as being both safe and effective in 1956.<sup>44</sup> Under the 1962 Kefauver-Harris Drug Amendments the FDA was now responsible for reviewing the claims of drug manufacturers for all drugs.<sup>45</sup> Upjohn was required to submit a report including the “best available data to support medical claims.”<sup>46</sup> Upjohn objected to this directive and instituted an action against Robert H. Finch, Secretary of Health, Education & Welfare, and Herbert L. Ley, Jr., Commissioner of Food and Drugs.<sup>47</sup> Upjohn claimed that this standard of ‘substantial evidence’ applied only to new drugs considered by the FDA, not for products already in the

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38. *Kefauver-Harris Amendments Revolutionized Drug Development*, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm>.

39. *Id.*

40. *Id.*

41. *Id.*

42. *Id.*

43. 21 C.F.R. §141 (c) (1955)21 C.F.R 146 (c) (1955).

44. *Upjohn Co. v. Finch*, 422 F.2d 944, 948 (6th Cir. 1970).

45. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 36.

46. *Id.* at 948.

47. *Id.* at 949.

already in the marketplace.<sup>48</sup> The court disagreed by reasoning that the FDA had properly applied the Congressional definition in the 1962 amendments.<sup>49</sup> Upjohn further claimed that even if the substantial evidence requirement was warranted, they had met that requirement through their documents submission.<sup>50</sup> Most of the documents were testimonial in nature touting the commercial success of the drug.<sup>51</sup> The court concluded that these testimonials did not reflect “adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drugs involved” as required by the statute.<sup>52</sup>

Besides drug efficacy, in 1971 the FDA flexed its regulatory muscle when the agency required the first patient package insert for oral contraceptives.<sup>53</sup> The insert was required to contain information about specific risks and benefits so as to better inform the consumer.<sup>54</sup> In 1972 the Over-the-Counter Drug Monograph Review was initiated to ensure safety, effectiveness and proper labeling of drugs sold without a prescription.<sup>55</sup>

### **1980s Tamper Resistant Packaging and Prescription Drug Marketing**

In 1982 the FDA again issued broad sweeping regulations requiring tamper-resistant packaging to prevent poisoning deaths.<sup>56</sup> In 1984, the FDCA, the organic statute empowering the FDA to promulgate Congressional directives, was amended.<sup>57</sup> The Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) amended the FDCA to expedite the availability of less costly generic drugs by permitting FDA to approve applications to

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48. *Id.* at 951.

49. *Id.*

50. *Id.* at 954.

51. *Id.*

52. *Id.* Upjohn had submitted over 50 documents.

53. *100 Years of Protecting and Promoting Women’s Health*, <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/ucm118458.htm> (last accessed July 4, 2012).

54. *Id.*

55. ROSEANN B. TERMINI, *FOOD AND DRUG LAW FEDERAL REGULATION OF DRUGS, BIOLOGICS, MEDICAL DEVICES, FOODS, DIETARY SUPPLEMENTS, COSMETICS, VETERINARY AND TOBACCO PRODUCTS* at 9 (7th ed. 2014).

56. *100 Years of Protecting Women’s Health*, *supra* note 53.

57. Hatch-Waxman Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (1984).

market generic versions of brand-name drugs without repeating the research done to prove them safe and effective.<sup>58</sup> The Hatch-Waxman Act also permitted brand-name companies to apply for up to five years additional patent protection for the new medicines they developed to compensate for time lost while their products were undergoing the FDA approval process.<sup>59</sup>

In 1987 Congress enacted the Prescription Drug Marketing Act to address certain drug marketing practices that contributed to the diversion of large quantities of drugs in the secondary distribution market.<sup>60</sup> These practices presented the risk that mislabeled, adulterated, expired, and counterfeit drugs would enter the United States drug distribution system.<sup>61</sup> While this statute was not directed at drug manufacturers, it was intended to reign in the potentially suspect practices of many drug distribution companies.<sup>62</sup>

### **The Prescription Drug User Fee Act and the 1997 Landmark Modernization Act Legislation**

The Prescription Drug User Fee Act (PDUFA) was enacted to specifically address the need for more expeditious review periods for new drugs treating serious diseases.<sup>63</sup> PDUFA specifics will be further discussed in the upcoming section entitled, Value to Industry: The Prescription Drug User Fee Act (PDUFA). In 1997 Congress again amended the FDCA by enacting the Food and Drug Administration Modernization Act (FDAMA).<sup>64</sup> Directives of the FDMA included the “prompt approval of safe and effective drugs,” the reduction of review times for human drug applications and a commitment to implement more ambitious regulatory processes.<sup>65</sup> The ultimate mission was articulated as follows: “With the passage of FDAMA, Congress enhanced FDA’s mission in ways that recognized the Agency would be operating in a 21st century characterized by in-

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58. *Id.*

59. *Id.*

60. Prescription Drug Marketing Act of 1987, Pub. L. 100-293, 102 Stat. 95 (1988).

61. *Id.*

62. *Id.*

63. Prescription Drug User Fee Act of 1992, Pub. L. 102-571, 106 Stat. 4491 (1992).

64. Food and Drug Administration Modernization Act of 1997, Pub. L. 115-105, 111 Stat. 2296 (1997).

65. *Id.*

creasing technological, trade and public health complexities.”<sup>66</sup> From the perspective of even the most ardent proponents of the *laissez faire* approach to government intervention in the private sector, history alone justifies the existence of the Food and Drug Administration. Beginning in the early 20th century with the widespread adulteration of syrup and the deplorable conditions in the meatpacking industry, the absolute need for government intervention was evident. Self-regulation was apparently not sufficient enough at all levels in all industries to afford the luxury of a hands-off approach. Considering public outcry over early conditions as well as the public reaction to the near thalidomide disaster in the early 1960s, citizens also demanded action from those they elected to legislate in accordance with their notions of safety and well-being.

### The Present Day Climate of Continued Legislative Enactments

Fast forward ten years from FDAMA and Congress enacted the Food and Drug Administration Amendments Act (FDAAA) of 2007.<sup>67</sup> Over ten Titles in FDAAA concern drug regulation ranging from PDUFA to pediatric to advertising to post-market surveillance to name a few all with the stated goal of safety.<sup>68</sup> In 2012, the Biologics Price Competition and Innovation Act was enacted as part of the Patient Protection and Affordable Care Act.<sup>69</sup> The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012 by President Obama<sup>70</sup> This law, *inter alia*, sets forth a notification requirement to the FDA concerning drug shortages. The FDASIA also reauthorized the Prescription Drug User Fee Act (PDUFA).<sup>71</sup> While it exists to promulgate and enforce enacted legislation, the FDA has proactively called on Congress to leg-

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66. Food and Drug Administration Modernization Act (FDAMA) of 1997, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCA/SignificantAmendmentstotheFDCA/FDAMA/default.htm>. (last accessed July 1, 2012).

67. Food and Drug Administration Amendments Act of 2007, 121 Stat. 823 (2007)., *See* Roseann B. Termini, FOOD AND DRUG LAW FEDERAL REGULATION OF DRUGS, BIOLOGICS, MEDICAL DEVICES, FOODS, DIETARY SUPPLEMENTS, COSMETICS, VETERINARY AND TOBACCO PRODUCTS, at 7 (5th ed. 2012) .

68. *Id.*

69. Patient Protection and Affordable Care Act of 2010, Pub. L. No 111-148, 124 Stat. 119 §7001 (2010).

70. Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 3187 Sec. 101 (2012).

71. *Id.* at 1.

islate pursuant to its authority and expertise as an administrative agency.<sup>72</sup> To illustrate, the FDA focus on youth contributed to the enactment of the Family Smoking Prevention Tobacco Act (FSPTA), passed in 2009 after nearly 10 years of controversy in the judicial system.<sup>73</sup> The FDA must continue to call on Congress in order to successfully promulgate its ultimate goal as set forth in the FDCA; protecting the American public.

In a perfect world, all drug manufacturers would proactively implement stringent processes to ensure their products are both safe and effective. In the real world, most do. Unfortunately, one misstep is one too many when dealing with drug products intended for human absorption and ingestion. The point is that Congress enacted the FDCA and created the Food and Drug Administration to promulgate its mandates because the dynamic of a potentially unpredictable world of pharmaceuticals demands action from all parties empowered to act. The resultant climate is one where the private sector and the federal government are fully invested in ensuring that only safe and effective drugs make their way to the American consumer and patient. Striking a balance between a stagnant bureaucracy and a profit driven market will most probably remain a challenge. Part II of the analysis will expand on this topic by dissecting the nuances in the pharmaceutical industry and Food and Drug Administration interplay.

## **PART II: The Food and Drug Administration as Regulator, Watchdog, and Facilitator**

The Food and Drug Administration simultaneously acts as a regulator of federal law, a watchdog for the American healthcare system, and as a facilitator of drug research and development in the United States. The question of whether or not pharmaceutical companies would comply with federal law if Congress did not delegate regulatory authority to an administrative agency hinges on an examination of these three functions.

Ultimately, it would be next to impossible for pharmaceutical companies to comply with federal laws enacted to protect the public health in a way that would fully effectuate that mission without the

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72. Margaret A. Hamburg, Commissioner of Food and Drugs. Remarks at the Annual Conference of the Food and Drug Law Institute (Apr. 23, 2013) available at <http://www.fda.gov/NewsEvents/Speeches/ucm349118.htm>.

73. *Id.*

influence of the FDA. In several respects the FDA serves as constant reminder to drug companies that although they do exist to profit, their profits must always be tempered by an overall consciousness of their duty to provide safe and effective products to the American consumer.

Congress determined that the pharmaceutical industry could not and/or possibly at some point would not comply with federal law without a regulatory body to oversee and ensure compliance. A discussion focusing on the relationship between the pharmaceutical industry and the FDCA as it is carried out by the FDA interpretation of ‘prohibited acts’ and its subsequent issuance of warning letters, provides the basis for the conclusion that drug companies would be essentially lost without regulatory oversight.

The FDA issues both titled and untitled warning letters to serve as precursors to regulatory action under the FDCA. Ultimately, the question of whether companies would comply with the FDCA in the absence of a strong federal regulatory agency need not be addressed in this section because even *with* FDA oversight, drug companies could still potentially fail to adhere to the mandates of the FDCA. The succeeding section will explore the efficacy of self-regulation as it is effectuated through the Pharmaceutical Research and Manufacturers of America (PhRMA). Lastly, pharmaceutical legislation from Pennsylvania, New Jersey, and Delaware illustrate the fact that federal regulations inform and empower state action.

### **The Food and Drug Administration as Regulator in Fulfilling the FDCA Mandates of Enumerated Prohibited Acts**

The Food, Drug, and Cosmetics Act, the principal statute authorizing the FDA to promulgate Congressional mandates, enumerates prohibited acts.<sup>74</sup> By way of illustration, prohibited acts include the introduction of adulterated or misbranded drugs into interstate commerce, the adulteration or misbranding of any drug in interstate commerce, and the receipt of adulterated or misbranded drugs in interstate commerce.<sup>75</sup> A pharmaceutical company may read this section of the FDCA and be unclear as to what ‘misbranded’ means. The term itself is arguably ambiguous. The Code of Federal Regulations provides the necessary clarification by specifying the labeling re-

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74. 21 U.S.C. § 331 (2012).

75. *Id.*

quirements that drug companies must follow in order to comply with the FDCA.<sup>76</sup> For example, a drug or drug product is ‘misbranded’ under Title 21 if “the label does not bear conspicuously the name and place of business of the manufacturer,”<sup>77</sup> does not include a statement of ingredients,<sup>78</sup> or does not correctly place the expiration date on the label.<sup>79</sup> A drug may also be misbranded if the labeling contains ‘misleading’ statements.<sup>80</sup>

### **The Food and Drug Administration Issuance of Warning Letters Illustrative of Regulatory Efforts**

The FDCA delegates authority to the FDA to conduct inspections and investigations of potentially noncompliant conduct.<sup>81</sup> Further, the FDA is also authorized to issue warning letters termed titled and untitled depending on the severity of the alleged violation to pharmaceutical companies who are not in compliance with the mandates of the FDCA.<sup>82</sup> A warning “letter, FDA 483, meeting, telephone call” serves as notice by the FDA that a firm and or person is believed to be in violation of laws or regulations enforced by the FDA and they are allotted time to make corrections.<sup>83</sup> Warning letters give individuals and firms an opportunity to take voluntary action before the FDA initiates an enforcement action. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected.<sup>84</sup> The FDA’s view is that warning letters are issued only for violations of regulatory significance.<sup>85</sup> A Warning Letter is the agency’s principal means of achieving prompt

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76. 21 C.F.R. §201.2 (2012).

77. 21 C.F.R. § 201.1 (2012).

78. 21 C.F.R. § 201.10 (2012).

79. 21 C.F.R. § 201.17 (2012).

80. Among representations in the labeling of a drug which render such drug misbranded is a false or misleading representation with respect to another drug or a device or a food or cosmetic. 21 C.F.R. § 201.6 (2012).

81. 21 U.S.C. § 374 (2012).

82. U.S. Food and Drug Administration, *What is a Warning Letter?*, About FDA, <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194986.htm> (last visited Feb. 12, 2014).

83. *U.S. Food and Drug Admin., 6-2-Injunctions, Inspections, Compliance, Enforcement, and Criminal Investigations* FDA Administrative Enforcement, § 6:2 (2011), <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176734.htm> (last visited Feb. 12, 2014).

84. *Warning Letters supra* note 53

85. *Id.*

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and voluntary compliance with the Federal Food, Drug, and Cosmetic Act.<sup>86</sup>

Warning letters exemplify the regulatory and watchdog functions of the agency. The FDA website posts many of the warning letters that the agency has sent to drug companies concerning alleged violations. Query whether considering that companies are on notice that the FDA is authorized to conduct inspections<sup>87</sup> of its facilities and violations are detected implying that some *still* fail to comply with the FDCA mandates justifies the existence of a powerful oversight agency and whether all drug companies would comply without it.<sup>88</sup>

**Self-Regulation**

The above discussion draws the conclusion that the regulated industry might not necessarily comply with the Food, Drug, and Cosmetics Act without the strong regulatory presence of the Food and Drug Administration. The following section explores how and to what extent the pharmaceutical industry self-regulates depicting the Pharmaceutical Research and Manufacturers of America (PhRMA) as an illustration, and how this organization interacts with the FDA in pursuit of FDCA compliance.

Drug companies can proactively and without federal mandate employ many different measures to ensure that public safety is maintained so that the manufacturer remains reputable and as well as profitable. Yet, the reality is that most of the guidelines for ensuring public safety come from the federal government as embodied under the FDCA. The Pharmaceutical Research and Manufacturers of America illustrates this notion. PhRMA is an industry group whose directive is to promote self-regulation. The mission of the organization is to “conduct effective advocacy of public policies that encourage discovery of important new medicines for patients and pharmaceutical and biotechnology research companies.”<sup>89</sup> PhRMA directives include providing “broad access to effective medicines, strong intellectual property incentives and transparent regulation toward a free flow of

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86. *Id.*

87. 21 U.S.C. § 374 (2012).

88. *FDA Enforcement Statistics Fiscal Year 2011*, <http://www.fda.gov/downloads/ICECI/EnforcementActions/UCM285781.pdf> (last visited August 30, 2012).

89. *PhRMA Members are Leading the Way in the Search for New Medicines and cures*, <http://www.phrma.org/about> (last visited Feb. 17, 2014).

information to patients.”<sup>90</sup> Issues facing the pharmaceutical industry as PhRMA articulates them include drug safety, counterfeit drugs, and the ramifications of the Prescription Drug User Fee Act (PDUFA).<sup>91</sup> PhRMA asserts that pharmaceutical manufacturers are dedicated to educating the public about drug safety by improving its adverse event reporting system and ensuring that the drugs patients are taking have been thoroughly studied and evaluated in a series of clinical trials.<sup>92</sup>

Portions of the discussion surrounding PhRMA are reviewed under the forthcoming ‘Facilitator’ and ‘Watchdog’ sections. Analysis of PhRMA in this section illustrates the fact that most, if not all, attempts at self-regulation by drug companies remain inextricably intertwined with the FDA. For example, PhRMA provides resources to the FDA to ensure that drug safety data is evaluated effectively and efficiently.<sup>93</sup> PhRMA works with the FDA to educate the public about the risks associated with negative side effects of drugs that have already been approved and are available on the market.<sup>94</sup> PhRMA also clarifies that pharmaceutical companies play various roles in ensuring drug safety; (1) to stringently monitor clinical trials of new drugs and (2) monitor healthcare outcomes by reporting adverse events and/or negative side effects to the FDA.<sup>95</sup> As will be discussed in following sections, the FDA requires new drug testing.<sup>96</sup> While reporting adverse events is *voluntary* for consumers<sup>97</sup> the FDA *requires* drug and therapeutic biological product manufacturers, distributors, and packers to report adverse drug experience information.<sup>98</sup>

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90. *Id.*

91. *Id.*

92. *Id.*

93. For over 50 years, PhRMA and the FDA have worked together to ensure the safety and integrity of medicines, <http://www.phrma.org/fda-regulatory#sthash.ozmUSkOw.dpuf> <http://www.phrma.org/fda-regulatory> (last accessed April 10, 2014).

94. *Id.*

95. *What is the role of pharmaceutical companies in ensuring drugs safety?*, <http://www.sharecare.com/health/medical-research/pharmaceutical-companies-ensure-drug-safety> (last visited Feb. 12, 2014).

96. 21 C.F.R. § 314.1 (2012).

97. *FDA Adverse Event Reporting System (FAERS)(formerly AERS)*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> (last visited Feb. 12, 2014).

98. 21 C.F.R. § 314.80 (2012).

PhRMA makes wholly independent attempts at self-regulation by providing voluntary standards or what are known as “guiding principles” for drug companies to follow.<sup>99</sup> One such attempt concerns direct-to-consumer advertisements. In 2005 PhRMA created an “Office of Accountability”<sup>100</sup> encouraging consumers and healthcare professionals to comment on direct-to-consumer advertising campaigns. PhRMA also encourages companies to promote health and disease awareness as part of their marketing campaigns and to include information about drug assistance programs for uninsured and low-income patients.<sup>101</sup> These guidelines are not mandated by the FDA and some of the suggested standards actually exceed FDA requirements. Pursuant to PhRMA’s guiding principles, some in the pharmaceutical industry announced a voluntary ban on advertising its new drugs to consumers in their first year on the market.<sup>102</sup> This case study exemplifies that under some circumstances, a drug company will voluntarily set forth its own compliance standards. There have been cases, however, where companies have agreed to pay millions of dollars to settle multiple civil allegations of fraudulent marketing and pricing schemes at the expense of federal health care programs for the poor and the elderly.<sup>103</sup> Query whether voluntary guiding principles are sufficient to ensure public safety and consumer confidence. The skeptical public perception as shown by the fact that in 2006, only 9% of Americans believed drug companies were generally honest, reaffirms this notion.<sup>104</sup>

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99. *PhRMA Principles & Guidelines*, <http://www.phrma.org/principles-and-guidelines> (last visited Feb. 12, 2014).

100. *PhRMA’s Office of Accountability Receives Comments about DTC Advertisements for Prescription Medicines*, <http://www.phrma.org/office-of-accountability> (last visited Feb. 12, 2014).

101. *PhRMA Guiding Principles: Direct to Consumer Advertisements About Prescription Medicines*, <http://www.phrma.org/sites/default/files/pdf/phrmaguidingprinciplesdec08final.pdf>.

102. Act of Sep. 27, 2007, Pub. L. No. 110-85, 121 Stat. 823.

103. Press Release, Bristol-Myers Squibb to Pay More Than \$515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing (Sep. 28, 2007)(on file with the Department of Justice) [http://www.justice.gov/opa/pr/2007/September/07\\_civ\\_782.html](http://www.justice.gov/opa/pr/2007/September/07_civ_782.html).

104. 1 AM.JUR.2D *Pharmaceutical and Medical Device Litigation* §3:5 (2004).

### State and Local Regulatory Milieu

State and local governments legislate in ways that affect the food and drug regulated industry. States rely on the regulatory power of the Federal Food and Drug Administration when enacting laws with respect to new drugs and drug research. Pennsylvania, New Jersey, and Delaware have been selected to illustrate this point:

*New Jersey New Drug Statute:*

“No person shall introduce or deliver for introduction into intra-state commerce in the State of New Jersey any new drug unless (1) an application with respect thereto has become effective under the Federal Act,<sup>105</sup> or (2) an application filed pursuant to subsection b is effective with respect to such drug.”<sup>106</sup>

*Pennsylvania New Drug Statute:*

“No person shall sell, deliver, offer for sale, hold for sale, or give away, any new drug unless (i) an application with respect thereto has been approved or a notice of claimed investigational exemption for a new drug has been filed under the appropriate Federal act.”<sup>107</sup>

*Delaware Pharmaceutical Research Statute:*

“Prior to the participation of any patient in pharmaceutical research, the Department shall adopt rules and regulations governing such research. Such rules and regulations shall conform to the requirements of the Food and Drug Administration and to this chapter. In the course of promulgating such rules and regulations, the Department shall request the assistance of the Food and Drug Administration and the State Police Drug Diversion Unit and shall hold at least 1 public hearing.”<sup>108</sup>

State governments regulate through state legislation. They do not have a large oversight agency approximating the FDA to oversee the introduction of regulated products into their jurisdiction. Therefore, they rely on the authority and expertise of FDA as a far-reaching and powerful federal administrative agency to guide and empower their statutory provisions.

### The Food and Drug Administration as “Watchdog”

Every regulatory function that Congress delegates to the Food and Drug Administration through the Food, Drug, and Cosmetics Act

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105. 21 U.S.C.A. § 355 (West 2010).

106. N.J. STAT. ANN. § 24:6A-1 (West 1940).

107. 35 PA. CONS. STAT. §780-110 (1972).

108. DEL. CODE ANN. 16 § 5172 (2011).

could technically be labeled “watchdogging” because each function is driven by this singular directive, to ensure the safety of the American public through food and drug consumer protection.<sup>109</sup> This section will focus on premarket approval and postmarket surveillance of drugs. Premarket review under the FDA Center for Drug Evaluation and Research (CDER), postmarket surveillance under MedWatch, and FDA recalls, market withdrawals, and safety alerts will be discussed to arrive at the ultimate conclusion that the drug related industry could not comply with Congressional mandates without the regulatory presence of the FDA.

### **Illustration: The Premarket Review under The Center for Drug Evaluation and Research (CDER)**

The Center for Drug Evaluation and Research (CDER) serves as a consumer watchdog for the American healthcare system.<sup>110</sup> The CDER’s primary focus is to evaluate new drug applications as well as abbreviated new drug applications prior to product marketing.<sup>111</sup> CDER does not test drugs; this is the responsibility of the manufacturer.<sup>112</sup> Drug sponsors interested in marketing a new drug are required to submit what is called a New Drug Application or NDA<sup>113</sup> to CDER for evaluation. The NDA application is the ‘vehicle’ through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the United States.<sup>114</sup> The goals of the NDA are to determine whether the drug is safe and effective for its intended use, whether the labeling and packaging is appropriate, and whether the manufacturing process satisfactorily ensures the overall quality, purity, strength, and identity of the proposed drug.<sup>115</sup> CDER employs scores of physicians, statisticians, chemists,

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109. 21 U.S.C. § 393 (2012).

110. *FAQs about CDER*, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/FAQsaboutCDER/default.htm> (last accessed Feb. 12, 2014).

111. *Id.*

112. *Id.*

113. 21 C.F.R. § 314.1 (2012).

114. *New Drug Application (NDA)*, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/> (Feb. 12, 2014).

115. *Id.*

pharmacologists and other scientists to review NDA submissions.<sup>116</sup> Simply stated, a drug sponsor cannot market a new pharmaceutical without having satisfied the extremely stringent requirements set forth in the FDA New Drug Application procedures as reviewed by CDER. Without a strong administrative agency, the mandates enunciated in the Food, Drug, and Cosmetics Act could not be adequately fulfilled. This means that there would be no FDA to address the need for stringent approval processes regarding the sale and marketing of new drugs. Without the FDA there is no CDER and there is no NDA to direct the actions of drug sponsors wanting to sell a new product. The upcoming section regarding FDA recalls, market withdrawals, and safety alerts further illustrates the ultimate conclusion that regulated food and drug law firms such as those in the pharmaceutical industry could not sufficiently comply with the Congressional directives set forth in the FDCA without the FDA.

### **Illustration: Postmarket Surveillance Under MedWatch**

The FDA encourages consumers and healthcare professionals to report serious reactions, product quality problems, therapeutic failure, and product use errors with human medical products. MedWatch is a program created by the FDA to act as a reservoir and database for such concerns.<sup>117</sup> The FDA acknowledges that drugs approved through the CDER New Drug Application process may still cause adverse reactions serious enough for agency consideration.<sup>118</sup>

The FDA has conceded that while the public has been “welcome” to report side effects, product quality problems and other issues to MedWatch, the focus had always been more on encouraging reporting from health care professionals.<sup>119</sup> The MedWatch reporting form was subsequently created with the healthcare professional in

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116. *Jobs at the Center for Drug Evaluation and Research (CDER)* <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm081244.htm> (last visited Feb. 12, 2014).

117. *How Consumers Can Report an Adverse Event or Serious Problem to FDA*, <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053074.htm> (last visited Feb. 12, 2014).

118. FAQs about CDER, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/FAQsaboutCDER/default.htm> (last accessed July 1, 2012).

119. *WANTED: Consumers to Report Problems*, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm354560.htm> (last accessed June 21, 2013).

mind.<sup>120</sup> As a result, the public deemed the form too technical to utilize as a resource to notify the FDA of a particular concern.

In 2013, The FDA celebrates the 20th anniversary of MedWatch.<sup>121</sup> To commemorate the milestone, the FDA introduced a new consumer-friendly reporting form to facilitate and encourage public participation.<sup>122</sup> The FDA worked with the American Association of Retired Persons (AARP), Consumers Union, and the National Women's Health Network to develop its "Consumer Form."<sup>123</sup>

To further facilitate public participation in postmarket surveillance of approved drug products, the FDA has recently implemented a web-based learning tool called, MedWatchLearn. This tool is meant to educate all potential participants in postmarket surveillance on how to properly complete a report.<sup>124</sup>

The FDA has also incorporated social media platforms such as Twitter to both notify the public of recently reports concerns as well as encourage participation in voluntary reporting.<sup>125</sup> The FDA Twitter page provides "clinically important safety information on human medical products from FDA," and provides its followers a forum for comment and discussion.<sup>126</sup>

Public participation is both necessary and beneficial to promulgate the mission of the FDA. This conclusion is best exemplified with specific instances in which the public notified MedWatch of a postmarket concern which led to FDA corrective action. Consider the following:

Public reports led to a nationwide recall of a particular lot of pre-filled syringes,<sup>127</sup> and Public reports led to stronger product warning labels to alert the public that a particular testosterone gel should be covered after application so it wouldn't get on other

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120. *Id.*

121. *MedWatch Turns 20 and Looks Ahead*, <http://www.fda.gov/Safety/MedWatch/ucm353999.htm> (last accessed June 21, 2013).

122. *Id.*

123. *Id.*

124. MedWatchLearn, <http://www.accessdata.fda.gov/scripts/MedWatchLearn/> (last accessed June 21, 2013).

125. US FDA MedWatch, <https://twitter.com/FDAMedWatch> (last accessed June 21, 2013).

126. *Id.*

127. *How Your Reports Could Help*, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm354560.htm> (last accessed June 21, 2013).

people, as it was inadvertently harming children upon exposure.<sup>128</sup>

The FDA has acknowledged with the release of its Consumer Form that with the ubiquity of the internet and its near-infinite resources, the American public feels individually and collectively empowered to participate in the management of their own well-being and the well-being of the United States citizenry at large.<sup>129</sup> The new MedWatch form is a manifestation of that acknowledgement, and if not for the existence of the FDA, no such centralized database would exist for consumers and healthcare professionals to report serious reactions, product quality problems, therapeutic failure, and product use errors related to the drugs sold and distributed by the pharmaceutical industry. Corollary to the aforementioned efforts to encourage public participation is the release of the FDA Transparency Initiative, a program addressed in further detail in the forthcoming section entitled, Communication with Stakeholders: the FDA Transparency Initiative.

### **Illustration: Recalls, Market Withdrawals, and Safety Alerts**

As stated earlier, the FDA has the power to investigate pharmaceutical manufacturing facilities. The purpose of these investigations is to ensure that facilities are in compliance with the Food, Drug, and Cosmetics Act and accompanying federal regulations. Drug manufacturers for example have a built-in motivation to produce safe and efficacious products notwithstanding this authority- market reputation and profit. The point is that it is in the best interest of drug manufacturers to self-regulate in this context because without safe and effective products, drug firms would in essence self-destruct. So why does the FDA find it necessary to implement stringent approval processes and postmarket drug surveillance? History strongly suggests that although most companies would undertake appropriate precautions to ensure public safety, quackery and negligence can never be fully eradicated, thus justifying regulation and a strong regulatory body to promulgate laws.

By way of illustration, PhRMA defines the resulting relationship between the pharmaceutical industry and the federal government as follows: “The Food and Drug Administration has been a cornerstone

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128. *Id.*

129. *Id.*

in the fight to improve Americans' health. Due to the vital nature of the FDA's public health oversight, PhRMA stands behind an empowered agency that is adequately resourced through enhanced Congressional appropriations to conduct its crucial mission."<sup>130</sup>

One approach to illustrate the relationship is to explore recalls, market withdrawals, and safety alerts. While the FDA requires corrective and precautionary action, and in some instances has legislative recall authority, numerous food and drug law regulated manufacturers voluntarily recall and/or withdraw potentially harmful products in advance of federal mandates. Consider the following scenario:

Bedford Laboratories announced in 2012 a nationwide *voluntary* hospital/user level recall for Vecuronium Bromide due to particulate matter found in a small number of vials. Customers and healthcare practitioners were notified by the company to not use the product and quarantine it for immediate return.<sup>131</sup>

Similarly, Sandoz U.S. conducted a *voluntary* recall of its generic oral contraceptive Introvale® in the United States because of a packaging flaw.<sup>132</sup> Consumers reported that certain pills were mistakenly packaged in the incorrect blister card row. The company maintained that the possibility of serious adverse health consequences was remote, yet undertook the recall as a precautionary measure.<sup>133</sup> Through its press release, Sandoz encouraged consumers to report adverse events or health consequences relating to the recall to MedWatch.<sup>134</sup>

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130. *Resources Must Keep Pace with FDA's Increasing Responsibilities to Patients and Consumers*, PhRMA, available at <http://www.phrma.org/catalyst/alliance-for-stronger-fda-explains-sufficient-funding-critical> (last accessed April 2, 2014).

131. *Bedford Laboratories Issues Voluntary Hospital/User-Level Recall Of Vecuronium Bromide For Injection Preservative Free, Lot 2067134, Because Of Health Risk*, <http://www.fda.gov/Safety/Recalls/ucm310191.htm> (last accessed June 28, 2012). (Bedford Laboratories informed the FDA of its actions and stated that the firm was maintaining an ongoing discussion with the agency.)

132. *Sandoz US Announces Precautionary Recall Of Oral Contraceptive Introvale, Following Report Of Packaging Flaw*, <http://www.fda.gov/Safety/Recalls/ucm307098.htm> (last accessed June 29, 2012).

133. *Id.*

134. *Id.*

Finally, the Menz Club LLC conducted a *voluntary* recall of V Maxx Rx.<sup>135</sup> An FDA analysis of the product was found to contain undeclared sulfoildenafil. “Sulfoildenafil is an analog of sildenafil, an FDA approved prescription drug used to treat Erectile Dysfunction (ED), making V Maxx Rx, an unapproved new drug.”<sup>136</sup>

According to their press releases, the Bedford Laboratories and Sandoz U.S. recalls were precipitated by in-house investigations and direct consumer notification.<sup>137</sup> The Menz Club LLC recall was precipitated by an FDA investigation.<sup>138</sup> All three companies list each of its respective recalls as ‘voluntary.’ On the strength of both proactive and federally mandated actions, all three companies ‘voluntarily’ removed potentially dangerous drug from the marketplace.

If Bradford Labs and Sandoz had not removed each of its potentially compromised products, consumer complaints to MedWatch would likely have informed the FDA and led to an investigation, the likely result being a “voluntary” recall by each of the manufacturers. In these two cases, both manufacturers self-regulated and watchdogged themselves into removing products that they considered potentially dangerous to their customers. Menz Club LLC “voluntarily” removed its product subsequent to FDA notification. The ultimate inquiry with respect to whether pharmaceutical manufacturers would comply with federal law nevertheless remains. The strong inference is that good business practices and general ethical principles drive these companies to ensure that their products are simultaneously safe and profitable. Yet, justification of the necessity for “an FDA as a watchdog over the actions of all FDA regulated companies” remains stalwart.

### The Food and Drug Administration as Facilitator

As stated previously, the FDA does not develop or manufacture drugs. It is the express responsibility of drug firms to conduct research and clinical trials in order to gain FDA approval for a new

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135. *The Menz Club, LLC Issues a Voluntary Nationwide Recall of V Maxx Rx due to Undeclared Sulfoildenafil*, <http://www.fda.gov/Safety/Recalls/ucm305795.htm> (last accessed June 29, 2012).

136. *Id.*

137. *Bedford Laboratories supra* note 131; *Sandoz supra* note 132.

138. *The Menz Club, LLC supra* note 135.

drug,<sup>139</sup> investigational new drug,<sup>140</sup> or generic drug.<sup>141</sup> This section explores the Center for Drug Evaluations and Research (CDER) as it operates under federal regulations as a *facilitator* to pharmaceutical manufacturers eager for FDA approval, and the implications of the Prescription Drug User Fee Act (PDUFA)<sup>142</sup> as it relates to expediting this process. Also explored is the FDA Transparency Initiative, a program launched in June 2009 by the Commissioner of the U.S. Food and Drug Administration, Dr. Margaret A. Hamburg in an effort to facilitate improved communication with pharmaceutical companies and the public.

### **Illustration: The Center for Drug Evaluation and Research (CDER) as ‘Facilitator’**

Through the Center for Drug Evaluation and Research (CDER), the FDA facilitates this approval phase by providing regulatory guidance to pharmaceutical manufacturers regarding applications to market new, investigational, and generic or “abbreviated new drugs.”<sup>143</sup> For example, current federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state line.<sup>144</sup> Since a sponsor will most likely ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The Investigative New Drug Application is the means through which the sponsor technically obtains this exemption from the FDA.<sup>145</sup>

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139. 21 C.F.R. § 310.3 (2012) (New drug substance means any substance that when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance.)

140. 21 C.F.R. § 312.3 (2012) (Investigational new drug means a new drug or biological drug that is used in a clinical investigation.)

141. 21 C.F.R. § 314.4 (2012) (Authorized generic drug means a listed drug, as defined in this section, that has been approved under section 505(c) of the act and is marketed, sold, or distributed directly or indirectly to retail class of trade with labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trademark that differs from that of the listed drug).

142. Prescription Drug User Fee Act Reauthorization, Pub. L. No. 112-144, (2012).

143. 21 C.F.R. § 314.50 (2012).

144. 21 C.F.R. § 312.

145. 21 C.F.R. § 312.2 (2012).

In essence, the FDA watchdogs the actions of pharmaceutical manufacturers under the guise of facilitation. A facilitator is one that helps to generate an outcome (as learning, productivity, or communication) by “providing indirect or unobtrusive assistance, guidance, or supervision.”<sup>146</sup> While CDER does not directly supervise the actions of drug sponsors, the requirements for FDA approval are so specific and detailed that a pharmaceutical manufacturer wishing to market a new drug cannot follow but one path to that end.<sup>147</sup> The Code of Federal Regulations is that path. In this regard, the FDA, through CDER, is less a facilitator than a premarket watchdog.<sup>148</sup>

### **Value to Industry: The Prescription Drug User Fee Act (PDUFA)**

Through CDER, the FDA employs one of the most stringent drug approval processes in the world. The strictness of the process is intended to maximize the safety of the drugs that become available to American citizens.<sup>149</sup> One of the potentially negative byproducts of such stringency is the delay in getting approval for a drug that addresses a serious disease. According to CDER, “determining whether a disease is serious is a matter of judgment, but generally is based on the following; whether the drug will have an impact on factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”<sup>150</sup> AIDS, Alzheimer’s, heart failure, cancer, epilepsy, depression and diabetes serve as examples.

In 1992 Congress addressed this issue by amending the Federal Food, Drug, and Cosmetic Act to authorize prescription drug product fees.<sup>151</sup> Congress found that the approval of safe and effective drugs

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146. Merriam-Webster Online Dictionary. <http://www.merriam-webster.com/dictionary/facilitator?show=0&t=1392955849> (last accessed June 25, 2012).

147. 21 C.F.R. § 314.50 (2012).

148. *Id.*

149. Margaret A. Hamburg, M.D. Remarks at the Annual Conference of the Food and Drug Law Institute, April 23, 2013, 68 FOOD AND DRUG L. J. 217 (2013). (Yet drug approvals have risen. In 2012, the FDA approved 39 novel drugs which was the most in a decade.)

150. *Fast Track, Breakthrough therapy, Accelerated Approval and Priority Review*, <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (last accessed June 28, 2012).

151. Prescription Drug User Fee Amendments of 2002, Pub. L. No 102–571, 106 Stat 4491.

was critical to improving the public health. To that end, additional funds were deemed necessary to augment FDA resources devoted to the process for review of human drug applications.<sup>152</sup> The fees authorized in the amendment were to be dedicated to expediting the review of human drug applications. The Prescription Drug User Fee Act (PDUFA) authorizes the FDA to collect fees from companies that produce certain human drugs and biological products. There are three types of user fees: application fees,<sup>153</sup> establishment fees,<sup>154</sup> and product fees.<sup>155</sup>

Along with addressing the standard review time,<sup>156</sup> the FDA has developed three approaches to making drugs available as rapidly as possible; Priority Review, Fast Track Approval, and Accelerated Approval.<sup>157</sup> Priority review applies to all products that have the potential for providing a significant treatment, preventive or diagnostic therapeutic advance.<sup>158</sup> Products regulated by CDER are eligible for priority review if they provide a significant improvement compared to marketed products in the treatment, diagnosis, prevention or treatment of a disease.<sup>159</sup> Fast track drug development programs are designed to facilitate the development and expedite the review of drug and biological products that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address

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152. *Id.*

153. *Id.* (A prescription drug establishment fee applies to each person that owns a prescription drug establishment, at which is manufactured at least one prescription product) .

154. *Id.* (A prescription drug application fees applies to those drugs requiring submission of a human drug application to the FDA.)

155. *Id.* (A prescription drug product applies to drugs that specify strength or potency in final dosage for which a human drug application has been approved, and which may be dispensed only under prescription.)

156. *Fast Track, Breakthrough Therapy Accelerated Approval and Priority Review*, <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (last accessed June 28, 2012). (Standard Review is applied to a drug that offers at most, only minor improvement over existing marketed therapies. The 2002 amendments to PDUFA set a goal that a Standard Review of a new drug application be accomplished within a ten-month time frame.)

157. *Guidance for Industry Available Therapy*, <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf> (last accessed July 1, 2012).

158. *Id.*

159. *Id.*

unmet medical needs.<sup>160</sup> The accelerated approval process applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.<sup>161</sup>

In addressing whether the pharmaceutical industry would comply with Congressional mandates without the FDA in this context, the focus is not on analyzing violative activities, rather it is about exemplifying how regulation and subsequent compliance can achieve a unified end despite, at least facially, mutually exclusive goals. In 1992 Congress deemed the FDA approval process to be ineffective in protecting the health of American citizens and consequently, PDUFA empowered the FDA to collect fees from pharmaceutical companies to bolster approval resources toward providing safe drugs to patients and consumers.<sup>162</sup> From the industry standpoint, drug firms were now obligated to pay for something that benefited them in the end; an expedited process for product entry into the marketplace.

To illustrate the relationship between Congress, the FDA, and the pharmaceutical industry, an analogy is in order; consider a delivery truck carrying cargo for company X from point A to point B. This truck is required by Group Y, who represents those in need of that cargo, to pass through a very long and winding passage. Company X wants to deliver that cargo quickly so they can make a profit and Group Y wants that cargo delivered quickly to fulfill the needs of those they represent. What to do? Group Y requires company X to pay a fee to its road crew who will shorten the length of the existing road. If the fee exceeded the profit, there is no incentive to comply with the requirement. Yet, if the fee ensures a profit and facilitates more cargo passage, everyone wins. Of utmost important in this scenario is the efficiency of the road crew shortening the road.

Group Y obviously represents the FDA in the above analogy. The most important determination, therefore, is whether PDUFA fees have successfully “shortened the road.” Considering the following statistics:

1993 (Pre-PDUFA):

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160. *Id.*

161. 21 C.F.R. § 314.50 (2012).

162. *Id.*

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1993 (Pre-PDUFA):

Submission Type	Number Approved	Median FDA Review Time (months)
NDA Standard	12	27.2
NDA Priority	13	13.9

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2011 (note that the FDA has since implemented Performance Goals relating to review times):

Submission Type	Number Filed	2011 Performance Goal	Actual Performance
NDA Standard	77	90% in 10 months	100%
NDA Priority	23	90% in 6 months	96%

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Taking into account the fact that standard review times have been cut by nearly two-thirds and priority review in better than half over the past 18 years, the obvious conclusion is that the fees collected through PDUFA have successfully addressed the issues surrounding lengthy review periods. On July 9, 2012 President Obama signed into law Senate Bill 3187, Pub. L. No. 112-144,<sup>165</sup> the Food and Drug Administration Safety and Innovation Act (FDASIA). This law reauthorized the Prescription Drug User Fee Act (PDUFA). It is the fifth authorization of PDUFA that includes Title I of FDASIA and the performance goals and procedures for PDUFA V and includes user fees for medical devices, brand name drug approvals, generic drugs and biotechnology products of \$6 billion over five years. The following statement by the Pharmaceutical Research and Manufacturers of America (PhRMA) affirms this conclusion:

“The Food and Drug Administration Safety and Innovation Act of 2012 reauthorizes several programs that are critical to public health and support of innovation, including the Prescription Drug User Fee Act (PDUFA). Reauthorization of PDUFA will enhance the consistency and efficiency of FDA’s human drug review program, and will help bring safe, effective, and innovative medicines to patients in a timely manner.”<sup>166</sup>

163. *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccessstoimportantnewtherapies/ucm128291.htm> (last accessed September 2, 2012).

164. John K. Jenkins, M.D., *CDER New Drug Review: 2011 Update* (2011), <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM282984.pdf>.

165. Pub. L. No. 112-144, (2012).

166. *PhRMA Statement Regarding Prescription Drug User Fee Act Reauthorization*, <http://www.phrma.org/media/releases/phrma-statement-regarding-prescription-drug-user-fee-act-reauthorization-3> (last accessed June 29, 2012).

The intent of the Prescription Drug User Fee Act is to address a public need that simultaneously grants the private sector something it desires. While pharmaceutical manufacturers are obligated to comply through various fees under PDUFA, they would likely have voluntarily contributed investment capital toward a speedier review period with or without federal mandates. In this regard, the fee is less a charge for the privilege of a more expeditious review process and more an agreed upon system of collection toward the uniform goal of granting the American patient/consumer faster access to critical drug therapies.

### **Communication with Stakeholders: the FDA Transparency Initiative**

Pursuant to the Open Government Initiative<sup>167</sup> of the Obama Administration, the FDA released its Transparency Initiative with the express goal of improving communication with both stakeholders and the public.<sup>168</sup> President Obama has called for agencies to make publicly available compliance information more easily accessible, downloadable, and searchable online. In response, the FDA released a report that contained eight (8) draft proposals to improve access to its compliance and enforceable data.<sup>169</sup> On January 31, 2012, all eight (8) proposals were adopted.<sup>170</sup> These initiatives include the improvement of data quality and more timely data disclosure, the improvement of inspection database webpages, and an improved graphic presentation of FDA compliance and enforcement data.<sup>171</sup> The foregoing analysis exemplifies that the FDA recognizes the importance of

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167. *Open Government Initiative*, <http://www.whitehouse.gov/open> (last accessed October 1, 2013).

168. *FDA Transparency Initiative*, <http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm> (last accessed October 1, 2013).

169. *Draft Proposals for Public Comment to Increase Transparency by Promoting Greater Access to the Agency's Compliance and Enforcement Data*, <http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM273145.pdf> (last accessed October 2, 2013).

170. *Report on Exploratory Program to Increase Access to the Agency's Compliance and Enforcement Data* <http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM289490.pdf> (last accessed October 2, 2013).

171. *Report on Exploratory Program to Increase Access to the Agency's Compliance and Enforcement Data* <http://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM289490.pdf> (last accessed October 2, 2013).

communication with the regulated community. More precisely, the FDA recognizes that pharmaceutical companies must be put on notice of FDA expectations in order to effectuate its ultimate goal of protecting the American public.

## **Conclusion**

Congress established the Federal Food and Drug Administration and subsequently enacted the Food, Drug, and Cosmetics Act to, among other objectives, ensure that food and drug related companies conduct themselves in a manner focused at all times on the safety of the American public. Most firms would in fact conduct themselves in this manner with or without the threat of government intervention. Even if the single goal of the regulated industry is understandable profit, the most cynical would concede that the goal would be impossible to achieve without providing safe and effective products to patients and consumers.

The regulated industry should comply with Congressional mandates toward public safety without FDA oversight. They should self-regulate toward consumer safety without Congressional mandates; their financial stability depends on it. However, most important in drawing the ultimate conclusion that a pharmaceutical industry without strong and far-reaching regulatory oversight is not viable is the fact that no margin of error is acceptable when developing and marketing pharmaceuticals to the public for the express purpose of facilitating wellness.

The charge of this analysis is to determine whether or not the food and drug related industry specifically addressed by reference to the pharmaceutical industry's compliance with federal law in the absence of the FDA. The conclusion is that most would. However, 'most' is not enough. Consider the fact that the 1937 sulfanilamide disaster was the result of a compliance issue. Further, consider the fact that were it not for the dogged resolve of Dr. Frances Kelsey, thalidomide would have been approved in 'compliance' with federal regulations.

The stakes are simply too elevated for the American public in the context of pharmaceuticals. Perfection exemplified in the availability of absolutely safe and effective drugs for all citizens regardless of age, gender, predisposition, susceptibility, and a myriad of other potentially contributory factors is an impossible standard for the

pharmaceutical industry to meet. Body chemistry unique to each of its consumers cements this impossibility. This does not, however, relieve pharmaceutical manufactures from their duty to provide the safest and most effective products possible. Nor does it relieve Congress, expressly empowered to provide for the public welfare, from legislating and delegating regulatory power to the FDA to that end.

Striking the appropriate balance between free enterprise principles and obligatory government intervention is the most debated component of the pharmaceutical manufacturer-FDA continuum. Those claiming overregulation suggest that drug approval stringency exceeds what is socially optimal based on the theory that the approval of harmful drugs reflects more negatively on the FDA than does the denial of beneficial drugs.<sup>172</sup> Conversely, those claiming that the FDA does not regulate enough allege that the pharmaceutical industry asserts undue influence on the FDA.<sup>173</sup>

Irrespective of individual frame of reference, an unrelenting focus on safety and efficacy from both the federal government and the private sector is the only acceptable standard by which pharmaceuticals can be marketed and sold to the American patient and consumer. It can be stated with confidence that few, if any, would argue that the FDA should not oversee the pharmaceutical industry. The ongoing and likely endless debate is driven by fundamental philosophical differences regarding the degree of interventional power exerted over private industry by the United States federal government, specifically the Federal Food and Drug Administration. The conclusion reached at this juncture is that FDA remains critical and vital for safe and effective drug products and the overall mission of protecting the American public.

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172. Michael R. Ward, *Drug Approval Overregulation*, Regulation (Sept. 1, 2012 11:30 AM). <http://www.cato.org/pubs/regulation/regv15n4/reg15n4e.html>.

173. Rosie Taylor and Jim Giles, *Cash Interests Taint Drug Advice*, NATURE (published online October 19, 2005) available at <http://www.nature.com/nature/journal/v437/n7062/full/4371070a.html>, (FDA panels writing clinical guidelines on prescription drug usage contained at least one member with financial links to drug companies whose products were covered by those guidelines.).