

NOTE

TIME FOR A CHANGE: WHY THE FDA SHOULD REQUIRE GREATER DISCLOSURE OF DIFFERENCES OF OPINION ON THE SAFETY AND EFFICACY OF APPROVED DRUGS

I. INTRODUCTION

The United States is no stranger to pharmaceutical medicine scandals and tragedies. In the past fifty years, a number of “good drugs” have “gone bad,” resulting in severe effects for the patients who took them and leading to huge class action and products liability lawsuits. In 1971, a study confirmed the damaging effects of diethylstilbestrol, or DES, a synthetic estrogen drug given to pregnant women from 1941-1971 to help prevent miscarriages.¹ Many daughters of the women who took DES have been diagnosed with a rare vaginal cancer and show an increased risk of developing breast cancer, along with other fertility problems.² Many sons of the women who took DES have been diagnosed with testicular cancer and other reproductive system disorders.³ Additionally, negative effects of DES have appeared in the grandchildren of the women who originally took the drug.⁴

In the mid-late 1980s, enough reports of adverse reactions to Parlodel (the brand name of the drug bromocriptine) prompted the FDA to request that the manufacturer warn consumers.⁵ Many women who had taken the drug to prevent postpartum lactation subsequently suffered strokes, seizures, and heart attacks. The manufacturer, Sandoz Pharmaceuticals, denied the correlation and fought the FDA until 1994, when it finally “voluntarily” withdrew the drug’s indication for the prevention of lactation, but only after the FDA began official proceedings to withdraw approval of the drug.⁶ In 1997, the FDA withdrew fenfluramine, one of the active ingredients in “Fen-phen,” an

1. Sue McGrath, *Only a Matter of Time: Lessons Unlearned at the Food and Drug Administration Keep Americans at Risk*, 60 FOOD & DRUG L.J. 603, 605-06 (2005); John Travis, *Modus Operandi of an Infamous Drug*, SCI. NEWS, Feb. 20, 1999, at 124, 124.

2. McGrath, *supra* note 1, at 605; Travis, *supra* note 1, at 124.

3. McGrath, *supra* note 1, at 605; Travis, *supra* note 1, at 124.

4. McGrath, *supra* note 1, at 605.

5. Margaret A. Berger & Aaron D. Twerski, *From the Wrong End of the Telescope: A Response to Professor David Bernstein*, 104 MICH. L. REV. 1983, 1987 (2006).

6. *Id.* at 1987-88.

anti-obesity medication, from the market.⁷ The weight-loss “wonder drug” was shown to cause serious heart-valve problems in many patients.⁸

One of the more recently publicized “bad drug” scandals involved the arthritis pain medication drug rofecoxib (known under its brand name—Vioxx).⁹ Approved by the FDA in 1999,¹⁰ rofecoxib was part of a new class of non-steroidal anti-inflammatory drugs (“NSAIDs”), a cyclooxygenase-2 or “COX-2” inhibitor.¹¹ This class of drugs works to selectively inhibit COX-2 enzymes, reducing pain at the site of an injury or inflammation, but without inhibiting COX-1 enzymes, which protect the stomach lining.¹² Rofecoxib, along with other drugs in its class, such as celecoxib¹³ and valdecoxib,¹⁴ is different from other NSAIDs, such as ibuprofen¹⁵ and naproxen,¹⁶ because of the selectivity of the COX-2

7. U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., Questions and Answers About Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux), <http://www.fda.gov/cder/news/phen/fenphenqa2.htm> (last visited Sept. 27, 2007). This resulted in the withdrawal of two approved prescription drugs, Pondimin and Redux, that contained fenfluramine compounds as active ingredients. *Id.* The combination of either drug with another prescription medication, phentermine, was commonly known as “fen-phen” and was considered an off-label use by the FDA, as the combination had never received FDA approval. *Id.* After releasing reports on the detrimental effects of these drugs, the manufacturers voluntarily withdrew them from the market. *Id.*

8. *Id.*; see also Kate Cohen, *Fen Phen Nation*, FRONTLINE, Nov. 13, 2003, <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/hazard/fenphen.html>.

9. Due to the widespread publicity on the Vioxx scandal, this Note will present only a brief synopsis of the relevant events. A plethora of information is available on this topic. For more detailed and thorough examinations of events prior to Merck’s withdrawal of the drug, and other allegations of wrongdoing by the company, see *FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the S. Comm. on Finance*, 108th Cong. 1-3 (2004) [hereinafter *FDA, Merck and Vioxx*] (statement of David J. Graham, M.D., M.P.H., Associate Director for Science, Office of Drug Safety, Center for Drug Evaluation and Research, U.S. Department of Health and Human Services, Food and Drug Administration), available at <http://finance.senate.gov/hearings/testimony/2004test/111804dgttest.pdf>; John Abramson, *The Reliability of Our Medical Knowledge as a Product of Industry Relationships*, 35 HOFSTRA L. REV. 691, 701-02 (2006); Ronald M. Green, *Direct-to-Consumer Advertising and Pharmaceutical Ethics: The Case of Vioxx*, 35 HOFSTRA L. REV. 749, 751-59 (2006); W. John Thomas, *The Vioxx Story: Would It Have Ended Differently in the European Union?*, 32 AM. J.L. & MED. 365, 365-73 (2006); Anna Wilde Mathews & Barbara Martinez, *Warning Signs: E-mails Suggest Merck Knew Vioxx’s Dangers at Early Stage*, WALL ST. J., Nov. 1, 2004, at A1; Rita Rubin, *How Did Vioxx Debacle Happen?*, USA TODAY, Oct. 12, 2004, at 1-D; Eric J. Topol, Op-Ed., *Good Riddance to a Bad Drug*, N.Y. TIMES, Oct. 2, 2004, at A15.

10. Thomas, *supra* note 9, at 365; Rubin, *supra* note 9.

11. See Green, *supra* note 9, at 751-52; Thomas, *supra* note 9, at 368.

12. See Thomas, *supra* note 9, at 368.

13. Known under the brand name “Celebrex.” About.com: Arthritis, Q&A: FDA Regulatory Actions on COX-2 Inhibitors & NSAIDs, <http://arthritis.about.com/od/arthritismedications/a/qafdaactions.htm> (last visited Sept. 1, 2007) [hereinafter About.com: Arthritis].

14. Known under the brand name “Bextra.” *Id.*

15. Known under the brand names of “Advil” and “Motrin,” among others. *Id.*

16. Known under the brand names of “Aleve” and “Anaprox,” among others. *Id.*

enzyme.¹⁷ The non-selective NSAIDs inhibit both COX-2 and COX-1 enzymes, and can therefore have a negative effect on the stomach lining, causing upset stomachs or ulcers. Thus, COX-2 inhibitors provide pain relief without the negative effects to the stomach and gastrointestinal system.¹⁸

Once approved by the FDA, Vioxx quickly became a “blockbuster drug” for its manufacturer, the Merck Company. In 2003, sales of Vioxx totaled \$2.5 billion, and from May 1999 through August 2004, more than 100 million prescriptions were filled in the United States.¹⁹ Unfortunately, COX-2 inhibitors turned out to have some unwelcome side effects. In 2000, a post-approval study (known as the VIGOR study) comparing the adverse effects of rofecoxib to those of naproxen in arthritis patients was completed by Merck and published in the *New England Journal of Medicine* (“*NEJM*”).²⁰ This study indicated a four times greater risk of heart attack in patients treated with rofecoxib than in those patients treated with naproxen.²¹ In response, Merck argued to the FDA that the VIGOR study actually showed a beneficial aspect of naproxen, rather than a detrimental effect of Vioxx.²² In 2001, the *Journal of the American Medical Association* (“*JAMA*”) published results from a team of researchers showing that, compared to naproxen, Vioxx had a five times greater heart attack risk.²³ Merck again denied the allegations, claiming that the JAMA study was “flawed,” and Merck continued to aggressively market the drug.²⁴ Despite a variety of other studies indicating the increased risks of heart attack and stroke caused by Vioxx, it was not until 2004, when Merck undertook a study hoping to find that Vioxx could be used to treat colon polyps, that the pharmaceutical company finally acknowledged the cardiovascular risks of rofecoxib, and voluntarily removed Vioxx from the market.²⁵

17. See Thomas, *supra* note 9, at 368.

18. See *id.*

19. *Id.* at 365-66; Rubin, *supra* note 9; Topol, *supra* note 9.

20. Thomas, *supra* note 9, at 366, 369; Rubin, *supra* note 9. See generally Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1520 (2000) (the VIGOR study).

21. Bombardier et al., *supra* note 20, at 1523, 1526. Later analysis of the VIGOR study increased the risk of heart attack for those taking rofecoxib to five times higher than those taking naproxen. *FDA, Merck and Vioxx*, *supra* note 9, at 1-2; Mathews & Martinez, *supra* note 9.

22. *FDA, Merck and Vioxx*, *supra* note 9, at 1; Green, *supra* note 9, at 753-55; Mathews & Martinez, *supra* note 9; Rubin, *supra* note 9.

23. Topol, *supra* note 9.

24. Green, *supra* note 9, at 755-56; Thomas, *supra* note 9, at 366, 369-71; Mathews & Martinez, *supra* note 9; Rubin, *supra* note 9; Topol, *supra* note 9.

25. Green, *supra* note 9, at 756; Mathews & Martinez, *supra* note 9; Rubin, *supra* note 9; Topol, *supra* note 9.

Thousands of personal injury suits have been filed against Merck and thousands more are expected.²⁶ Merck's stock value has dropped more than thirty percent since it withdrew Vioxx from the market,²⁷ and liability estimates from the injuries caused by the drug range up to fifty billion dollars.²⁸

However, Vioxx is certainly not alone in the recent "bad drug" media reports. Other recent "bad drugs" include: the birth control patch Ortho Evra (alleged to increase the risk of blood clots and strokes, especially in young women, without adequate warning to consumers),²⁹ the cholesterol drug Baycol (withdrawn from the market due to reports of fatal rhabdomyolysis, a breakdown of skeletal muscle that can lead to acute renal failure),³⁰ and the anti-depression medication Paxil (whose manufacturer, GlaxoSmithKline, is alleged to have known and withheld information about increased suicidal behavior in young adults).³¹ Recently, reports have revealed that the diabetes drug Avandia, produced by GlaxoSmithKline, may increase a patient's risk of heart attack and other cardiovascular problems.³²

Perhaps the most terrifying aspect of the aforementioned "bad drug" cases is not that negative or harmful side effects were ultimately linked to the drugs, but the amount of time the drugs remained on the market *without adequate warning to the consumers*, after the manufacturers knew (or had reason to know) of either the dangerous risks or the general ineffectiveness of the drugs. Even though a study on DES was published in 1953 stating not only that the drug was *not* effective in the prevention of miscarriages (the main reason it was

26. See Thomas, *supra* note 9, at 366.

27. *Id.*

28. Michael Orey, *Presto: A New VIOXX Liability Estimate! Why Analysts' Reports Shift Wildly With Every Twist in Litigation Against Merck*, BUS. WK., Dec. 5, 2005, at 40.

29. Douglas & London, P.C. Files First Nationwide Ortho Evra Birth Control Patch Class Action Lawsuit, ORTHO EVRA INJURY, Aug. 18, 2005, <http://www.orthoevrainjury.net/index.html> (follow "News" hyperlink) [hereinafter ORTHO EVRA INJURY].

30. Defective Drugs FYI, Baycol, <http://www.defectivedrugsfyi.com/baycol.html> (last visited Oct. 9, 2007).

31. Marc J. Scheineson & M. Lynn Sykes, *Major New Initiatives Require Increased Disclosure of Clinical Trial Information*, 60 FOOD & DRUG L.J. 525, 533 (2005); Miranda Hitti, *Paxil Suicide Risk in Young Adults: FDA and Drug's Maker Warn Doctors of Possible Risk in Young Adults Aged 18-30*, WEBMD, May 12, 2006, <http://www.webmd.com/content/article/122/114571.htm>; Press Release, Office of New York State Attorney General, Settlement Sets New Standard for Release of Drug Information: Glaxo to Establish "Clinical Trials Register" with Information on All Company Drugs (Aug. 26, 2004), available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html [hereinafter Press Release, Glaxo].

32. Anna Wilde Mathews, *Sequel for Vioxx Critic: Attack on Diabetes Pill, Glaxo Shares Plunge as Dr. Nissen Sees Risk to Heart from Avandia*, WALL ST. J., May 22, 2007, at A1.

prescribed), but that it also may increase the risk of miscarriage, this indication for the drug remained until the FDA ordered its removal in 1971.³³ The FDA requested that Sandoz Pharmaceuticals warn consumers about the adverse reactions to Parlodel in 1985, and in 1989, the FDA Fertility and Maternal Health Drugs Advisory Committee found that use of Parlodel for lactation prevention was not particularly effective when compared to other means.³⁴ In response, Sandoz promoted the drug even more aggressively, and did not withdraw the indication for lactation prevention until 1994.³⁵ Studies in Europe linking one of the components of Fen-phen to primary pulmonary hypertension, an incurable and often fatal disease, existed before the FDA ever approved the combination drug.³⁶

It has been alleged that the manufacturers of the Ortho Evra birth control patch knew of the increased risks³⁷ of blood clots, heart attacks, and strokes before FDA approval of the drug in 2001, but failed to warn patients until the FDA mandated labeling changes in 2005.³⁸ GlaxoSmithKline withheld the results of at least four studies on Paxil, which allegedly showed the drug to be ineffective for the treatment of depression and an increased risk for suicidal behavior in young children, until a settlement agreement was reached in a suit by New York Attorney General Eliot Spitzer in 2004.³⁹ In the Vioxx case, Merck had reason to know of the increased risk of heart attacks as early as 2000,⁴⁰ but left the drug on the market until 2004.⁴¹

Since the 1800s, the federal government has responded to problems posed by the introduction of fake and harmful drugs into society by updating federal legislation and control on drugs and drug safety.⁴² In light of the Vioxx “scandal” and recent publicity surrounding other “bad

33. McGrath, *supra* note 1, at 605-06; Travis, *supra* note 1, at 124.

34. Berger & Twerski, *supra* note 5, at 1987-88.

35. *Id.* at 1988.

36. McGrath, *supra* note 1, at 614; Cohen, *supra* note 8.

37. As compared to oral contraceptives (i.e. “the pill”). ORTHO EVRA INJURY, *supra* note 29; *id.* (follow “Serious Risks” hyperlink).

38. ORTHO EVRA INJURY, *supra* note 29.

39. Press Release, Glaxo, *supra* note 31.

40. See Bombardier et al., *supra* note 20, at 1523, 1526 (publishing the results of the VIGOR study in November 2000). Some allege that Merck knew of the drug’s dangers prior to its application to the FDA for approval—as early as 1996. See Mathews & Martinez, *supra* note 9.

41. Topol, *supra* note 9. It has been estimated that more than 130,000 people were injured by Vioxx, with thirty to forty percent of that number probably having died, and thousands of which could have been avoided if the risks were acknowledged sooner. FDA, Merck and Vioxx, *supra* note 9, at 1-2. This number has been likened to the rough equivalent of 500 to 900 airplanes “dropping from the sky.” *Id.* at 2.

42. See *infra* Part II.

drugs,” and with the increased concerns that negative and dangerous effects of pharmaceutical drugs are being kept from consumers until the harm is done, it is time for another change in the federal drug policy. It is time for the FDA to acknowledge that studies and reports on the safety and efficacy of pharmaceutical drugs are subject to differences of medical opinion in their interpretation and analysis. It is time for the FDA to either provide, or require that the pharmaceutical industry provide, all of the scientifically supported interpretations to physicians and consumers. Greater transparency of these differences of opinion, including information on the stake each “opinion-holder” has in the outcome or success of the drug in question, will provide consumers with the information they need to make a truly educated choice about the drugs and medicines they place into their bodies.

Part II of this Note will follow the evolution of the federal drug legislation and will note its changes in response to (or at least influenced by) past medical tragedies and pharmaceutical scandals. This section will also track the labeling requirements of the various statutes, as labels are the primary means of providing prescribing physicians and their patients with important information on a drug’s risks and benefits. The importance of getting this information to physicians will be presented in a brief discussion of the learned intermediary doctrine. Part III will then examine *Bradley v. Weinberger*, a case centered on the FDA’s determination of proper labeling when a difference of opinion existed within the scientific community about the negative effects of a drug. This section will also review the recent changes in FDA regulations on label requirements, including electronic labels. Part IV will discuss some of the history of dealing with differences of opinion regarding the risks and benefits of pharmaceutical drugs in case law and legislative history, and will examine the need for a new policy favoring the individual consumer. Finally, Part v. will suggest changes to promote this new policy, and Part VI will provide a conclusion.

II. THE HISTORY OF FEDERAL DRUG LEGISLATION

A. *Nineteenth Century Food, Drug and Health Legislation*

The United States has had federal legislation protecting food for just over 100 years.⁴³ Health care legislation goes back more than 200

43. The first United States legislation to protect the integrity of food was enacted in 1883, to prevent the importation of adulterated tea. *See* Act of Mar. 2, 1883, ch. 64, 22 Stat. 451; PETER

years, to the National Marine Health Service Act of 1798.⁴⁴ This Act created a type of health care insurance plan for the nation's sailors, taking a certain portion of their pay,⁴⁵ and setting it aside "to provide for the temporary relief and maintenance of sick or disabled seamen, in the hospitals or other proper institutions now established in the several ports of the United States"⁴⁶ and to build hospitals "when necessary . . . for the accommodation of sick and disabled seamen."⁴⁷

Federal legislation on drug regulation did not begin until the early nineteenth century. In 1813, Congress passed legislation appointing a Vaccine Agent "to preserve the genuine [smallpox] vaccine matter, and to furnish [it] to any citizen of the United States, whenever it may be applied for, through the medium of the post office . . ."⁴⁸ The purpose behind this Act was to assure the dissemination of "a safe and effective supply of smallpox vaccine" throughout the United States, as a fake vaccine was being sold and could not be distinguished from the genuine vaccine.⁴⁹

In 1848, Congress then passed a law to prevent adulterated and spurious drugs from being imported into the United States.⁵⁰ This law provided that all imported "drugs, medicines, medicinal preparations . . . used wholly or in part as medicine" would be "examined and appraised" as to their "quality, purity, and fitness for medical purposes" before being released for commercial or medical purposes in the United States.⁵¹ The law also required that each parcel be marked with the name of the manufacturer of the item and the place of the preparation.⁵² While this law had overwhelming support in both the Senate and the House, some critics believed it was not enough to prevent importation of drugs without also preventing the manufacture and preparation of adulterated drugs here in the United States.⁵³ In 1879, a

BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW* 4 (2d ed. 1991). In comparison, England's earliest food regulation, prohibiting the adulteration of staple foods that were subject to price controls, was codified by Parliament in 1266. HUTT & MERRILL, *supra*, at 2.

44. Act of July 16, 1798, ch. 77, 1 Stat. 605.

45. *Id.* § 1.

46. *Id.* § 3.

47. *Id.* § 4.

48. Act of Feb. 27, 1813, ch. 37, 2 Stat. 806 (repealed 1822).

49. HUTT & MERRILL, *supra* note 43, at 7, 378, 660.

50. Act of June 26, 1848, ch. 70, 9 Stat. 237.

51. *Id.* § 1.

52. *Id.* § 2.

53. Representative Dickinson declared in the House Debates that this legislation was an "attempt[] to put the bell on the cat" and that he believed materials would just be brought into the United States, and spurious drugs would be manufactured here. HUTT & MERRILL, *supra* note 43, at 378-79 (citing CONG. GLOBE, 30th Cong., 1st Sess. 858 (1848)).

comprehensive, nationwide food and drug law was proposed⁵⁴ in response to publicity about adulteration of food and drugs that significantly raised public awareness.⁵⁵ Unfortunately, the states' rights side of the federalism argument prevented the acceptance of this law for more than twenty years.⁵⁶ From that point until the present, almost all major changes in federal food and drug legislation arose only after some scandal or tragedy had occurred to illustrate the need for greater protection.

B. *Tetanus Infected Diphtheria Antitoxin and the Biologics Control Act of 1902*

In the fall of 1901, thirteen children in St. Louis died after receiving a diphtheria antitoxin that was infected with live tetanus bacteria,⁵⁷ and another nine children died in Camden, New Jersey, supposedly from a contaminated smallpox vaccine.⁵⁸ In July of the next year, Congress enacted the Biologics Control Act of 1902,⁵⁹ also called the Virus, Serum, Toxin Law,⁶⁰ to ensure the purity and safety of serums and vaccines in the United States. Under this Act, in order to sell or trade (either nationally or internationally) any "virus, therapeutic serum, toxin,

54. *Id.* at 8.

55. In England, Fredrick Accum described various types of food and drug adulterations in his *Treatise on Adulterations of Food and Culinary Poisons* in 1820. Available at <http://www.gutenberg.org/etext/19031>; see HUTT & MERRILL, *supra* note 43, at 3. A report on public health in 1850 documenting lower life expectancy rates in America's large urban areas tagged the adulteration of food and drugs as a serious health concern. HUTT & MERRILL, *supra* note 43, at 7 (discussing LEMUEL SHATTUCK, REPORT OF THE SANITARY COMMISSION OF MASSACHUSETTS 1850, at 220-24 (Harv. U. Press 1948)). This problem was also illustrated in various United States publications, including *Frank Leslie's Illustrated Newspaper* and the *New York World*. *Id.* at 8.

56. See HUTT & MERRILL, *supra* note 43, at 8.

57. See *id.* at 8; Michael S. Labson, *Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients*, 6 J. HEALTH CARE L. & POL'Y 34, 34 (2002) (citing Ramunas A. Kondratas, *The Biologics Control Act of 1902*, in THE EARLY YEARS OF FEDERAL FOOD AND DRUG CONTROL 8, 14-15 (Glenn Sonnedecker ed., Am. Inst. of Hist. of Pharmacy 1982) [hereinafter Kondratas, *Biologics Control Act*]); Ramunas A. Kondratas, *Death Helped Write the Biologics Law*, FDA CONSUMER, April 1982, at 23, 24-25. The diphtheria antitoxin had been made from the blood of a horse infected by tetanus. Labson, *supra* at 34; Kondratas, *Biologics Control Act*, *supra* at 14.

58. Kondratas, *Biologics Control Act*, *supra* note 57, at 16.

59. The Biologics Control Act of 1902, Pub. L. No. 57-244, 32 Stat. 728 (1902) (codified at 42 U.S.C. § 262 (2000)).

60. Jeremy Grushcow, *The Ethics of Subject Selection for Testing Live-Attenuated HIV Vaccines*, 6 U. CHI. L. SCH. ROUNDTABLE 113, 116 n.16 (1999) (citing CHRISTINE GRADY, THE SEARCH FOR AN AIDS VACCINE: ETHICAL ISSUES IN THE DEVELOPMENT AND TESTING OF A PREVENTIVE HIV VACCINE 33 (Ind. U. Press 1995)).

antitoxin, or analogous product applicable to the prevention and cure of diseases of man,”⁶¹ the product must be prepared in an establishment that is duly licensed by the Secretary of the Treasury and each package of product must be marked with the product’s name, the manufacturer’s name, address and license number, and the expiration date of the product.⁶² The Act also prohibited anyone from falsely labeling a package containing any such biologic product,⁶³ and gave the Secretary of the Treasury, or any officer, agent or designated employee, the right to inspect any establishment used for propagation and preparation of such products.⁶⁴ Finally, the Act created a board of authority to promulgate rules to govern the issuance, suspension and revocation of licenses to establishments;⁶⁵ authorized the Secretary of the Treasury to direct and enforce the Act and any regulations created by the aforementioned board of authority;⁶⁶ and provided that violations of the Act would be punishable by a fine of not more than five hundred dollars or by imprisonment of not more than one year, or both at the discretion of the courts.⁶⁷ This law remains the basis of federal regulation of biological products for human use, and was updated in 1944 when the Public Health Service Act was enacted.⁶⁸ This Act served to “consolidate and revise the laws relating to the Public Health Service,”⁶⁹ and reorganized the Public Health Service into four divisions administered by the Surgeon General under the supervision of the Federal Security Administrator.⁷⁰

61. The Biologics Control Act of 1902 § 1.

62. *Id.*

63. *Id.* § 2.

64. *Id.* § 3.

65. The board was to be comprised of the Surgeon Generals of the Army, the Navy and of the Marine-Hospital Service, among others, and their authority was to be “subject to the approval of the Secretary of the Treasury.” *Id.* § 4. This board was called the Public Health and Marine Hospital Service and was essentially the progeny of the Marine Hospital Service, created by the National Marine Health Service Act of 1798, and would become the Public Health Service in 1912. U.S. Department of Health and Human Services, National Institutes of Health, *The NIH Almanac—Historical Data: Legislative Chronology*, http://www.nih.gov/about/almanac/historical/legislative_chronology.htm (last visited Oct. 11, 2007).

66. The Biologics Control Act of 1902 § 5.

67. *Id.* § 7.

68. HUTT & MERRILL, *supra* note 43, at 661. *See generally* Public Health Service Act, Pub. L. No. 78-410, 58 Stat. 682 (1944).

69. Public Health Service Act, Pub. L. No. 78-410, 58 Stat. 682 (1944).

70. *See id.* § 202.

C. *The Food and Drugs Act of 1906*

A book published in 1906 portraying the horrifying conditions in the stockyards of Chicago⁷¹ provided incentive for Congress to pass the Pure Food Act, establishing the government inspection of meat products,⁷² and the Federal Food and Drugs Act of 1906 (“F&D Act”),⁷³ also known as the “Wiley Act,”⁷⁴ forbidding “interstate commerce in adulterated and misbranded food and drugs.”⁷⁵ Under the F&D Act, drug products had to abide by the standards of purity and quality stated in the United States Pharmacopoeia and the National Formulary, or they had to meet the standards created by their manufacturers which were to be stated on the label of the product.⁷⁶ “Misbranding” under the F&D Act referred to statements made on the packages or labels that were false or misleading.⁷⁷ This Act authorized the seizure of any adulterated or misbranded products, and provided criminal penalties for violators in terms of fines and imprisonment.⁷⁸ However, the government could not prosecute those responsible for misbranding of drugs unless it could show intentional fraud,⁷⁹ and the law does not prevent a manufacturer from making fraudulent or misleading statements elsewhere than the label or package.⁸⁰

71. See UPTON SINCLAIR, *THE JUNGLE* (1906).

72. See Federal Food and Drugs Act, Pub. L. No. 59-384, 34 Stat. 768 (1906) *repealed by* 21 U.S.C. § 329(a) (1934) (the Pure Food Act, passed days earlier, was merged into the Federal Food and Drugs Act of 1906); see also PHILIP J. HILTS, *PROTECTING AMERICA’S HEALTH: THE FDA, BUSINESS, AND ONE HUNDRED YEARS OF REGULATION* 49-53 (2003) (describing how *The Jungle* motivated legislators to pass bill); McGrath, *supra* note 1, at 604.

73. Federal Food and Drugs Act, 34 Stat. at 768; HILTS, *supra* note 72, at 53-55; McGrath, *supra* note 1, at 604.

74. Dr. Harvey W. Wiley served as Chief Chemist of the United States Department of Agriculture’s Division of Chemistry (the “focal point” of food protection activities at that time) from 1883 to 1912. HUTT & MERRILL, *supra* note 43, at 4, 8-9. From 1902 to 1904, a group of twelve USDA employees known as “the poison squad” acted as human test subjects for various preservatives and common food additives, including boric acid, sulfurous acid, and formaldehyde (embalming fluid). *Id.* at 9. These studies played a large part in prompting Congress to finally pass the nationwide legislation, originally proposed in 1879, that regulated adulterated food and drugs. *Id.* at 8. For further details on Dr. Wiley and his “poison squad,” see HILTS, *supra* note 72, at 39-43.

75. Lauffer Hayes & Frank Ruff, *The Administration of the Federal Food and Drugs Act*, 1 LAW & CONTEMP. PROBS. 16 (1933), *reprinted in* HUTT & MERRILL, *supra* note 43, at 9, 9.

76. Federal Food and Drugs Act § 7. Because there were no standards available for food products, reference is made in the Act prohibiting the use of spoiled animal or vegetable products, use of substitutions that reduce the quality of the product, the hiding of damage to the product, and other such activities. See Hayes & Ruff, *supra* note 75, at 9.

77. Federal Food and Drugs Act § 8; Hayes & Ruff, *supra* note 75, at 9.

78. Federal Food and Drugs Act §§ 1-2; Hayes & Ruff, *supra* note 75, at 9.

79. McGrath, *supra* note 1, at 604.

80. HUTT & MERRILL, *supra* note 43, 11.

*D. Elixir of Sulfanilamide and the Food, Drug and
Cosmetic Act of 1938*

The next legislation protecting United States citizens from “bad drugs” was prompted by another medical tragedy. In the early 1900s, sulfa drugs were popular antibiotic drugs, especially the drug sulfanilamide.⁸¹ In 1937, the S.E. Massengill Company, one of many manufacturers of sulfanilamide in pill form, developed a liquid or syrup formula of the “wonder drug” for treating bacterial infections in infants and children.⁸² To create this liquid pediatric formula, the company combined the solid antibiotic with diethylene glycol to create “Elixir of Sulfanilamide.”⁸³ Within months of releasing the pediatric elixir, more than 100 people died from the poisonous content of the solution.⁸⁴

In the aftermath of this disaster, Congress passed the Federal Food, Drug, and Cosmetic Act of 1938 (“FD&C Act”),⁸⁵ the first federal regulation to require testing and proof of a drug’s safety before allowing its release into the market.⁸⁶ The FD&C Act prohibits the introduction into interstate commerce, and the delivery for introduction into interstate commerce, of any new drug unless the person or company has filed an application with the Secretary of Agriculture and that application is effective with respect to the drug.⁸⁷ The application itself consists of: a list of the drug’s components; a statement of the complete composition of the drug; a description of the methods used to manufacture, process and package the drug, including the facilities and controls used in each process; any samples of the drug or its components that the Secretary requests; samples of the proposed labeling for the drug; and most importantly, “full reports of investigations which have been made to show whether or not such drug is safe for use.”⁸⁸

The FD&C Act defines a “drug” as: those articles recognized in the

81. HILTS, *supra* note 72, at 89.

82. Labson, *supra* note 57, at 34; McGrath, *supra* note 1, at 604.

83. Today, diethylene glycol is known to be a lethal poison, and is used as the primary component of automobile antifreeze. Labson, *supra* note 57, at 34; McGrath, *supra* note 1, at 604.

84. Grushcow, *supra* note 60, at 116 n.16; McGrath, *supra* note 1, at 604. After learning of these deaths, most of whom were children, the elixir’s inventor took his own life. HILTS, *supra* note 72, at 92; Nancy E. Pirt, *Regulation of the Export of Pharmaceuticals to Developing Countries*, 25 DUQ. L. REV. 255, 259 (1987).

85. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301-397 (2000)).

86. This legislation was actually first introduced in 1933, but was not enacted until after the Elixir of Sulfanilamide deaths. HUTT & MERRILL, *supra* note 43, at 11-12; Labson, *supra* note 57, at 34.

87. See Federal Food, Drug, and Cosmetic Act § 505(a).

88. *Id.* § 505(b).

various official U.S. Pharmacopeias or supplements, or the National Formulary or supplements; those “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;” those articles “intended to affect the structure or any function of the body of man or other animals;” and the components of any of the above articles.⁸⁹ “New drug” is defined by the FD&C Act as any drug not generally recognized as safe (by those with training and experience in the evaluation of drug safety) for use under the conditions recommended, suggested or prescribed by the drugs’ labeling.⁹⁰

The FD&C Act also created stricter regulations of a drug’s labeling than had been provided in the F&D Act of 1906. Under the FD&C Act, “labeling” referred to “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”⁹¹ A drug was considered to be misbranded “[i]f its labeling [was] false or misleading in any particular”⁹² and *unless* its label contained “(1) adequate directions for use; and (2) such adequate warnings against use . . . where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application.”⁹³ While violations of the FD&C Act are still punishable by fines or criminal prosecution against guilty individuals or companies, the most common remedy is seizure of the unsafe or misbranded drug, and more recently, recalls of unsafe products.⁹⁴ The FD&C Act is still effective today, subject to various amendments.

E. *Thalidomide and the Kefauver-Harris Amendment*

The next significant change in federal drug legislation was prompted by the Thalidomide disaster in Europe. In the 1950s, two scientists working for a German drug company created thalidomide by combining two other harmless chemicals, and then tried to find a use for their new drug.⁹⁵ When it was discovered that the drug could be used to provide a deep and natural sleep without the negative side effects of

89. *Id.* § 201(g).

90. *Id.* § 201(p). The definition of “new drug” also includes those drugs that are recognized in investigations as safe for use under conditions prescribed or recommended by their labels, but that have not been used under such conditions for a material extent of time. *Id.*

91. *Id.* § 201(m).

92. *Id.* § 502(a).

93. *Id.* § 502(f).

94. Federal Food, Drug, and Cosmetic Act §§ 303(a), 304(a)-(b); HUTT & MERRILL, *supra* note 43, at 12-13.

95. See McGrath, *supra* note 1, at 606; see also TRENT STEPHENS & ROCK BRYNNER, DARK REMEDY: THE IMPACT OF THALIDOMIDE AND ITS REVIVAL AS A VITAL MEDICINE 8 (2001).

barbiturates, the drug company began selling thalidomide in Germany in 1956 and in England in 1958.⁹⁶ It was then discovered that thalidomide could be used to treat and control morning sickness in pregnant women.⁹⁷ This use of the drug became widespread in Europe, and shortly thereafter, occurrences of the rare birth defect phocomelia also became widespread.⁹⁸ The pediatrician in charge of the children's clinic at Hamburg University, Dr. Widukind Lenz, eventually connected the deformed infants to thalidomide taken by their mothers during pregnancy, and published his results in November 1961.⁹⁹

In the late 1950s, the German company responsible for thalidomide contracted with William S. Merrell Company ("Merrell") to sell thalidomide in the United States.¹⁰⁰ In September of 1960, Merrell submitted an application to the FDA for the approval of thalidomide, promoting the drug as a sedative and a treatment for a wide variety of medical and social problems.¹⁰¹ Under the FD&C Act at that time, human clinical trials did not need FDA approval, and before submitting its application, Merrell distributed pills to approximately 20,000 people in the United States.¹⁰² Because Merrell only had to prove the safety of the drug, and the German company's test on laboratory rats had produced no injurious effects,¹⁰³ Merrell had no reason to believe the drug application would not be approved, and planned to begin sales and distribution of the drug in March of 1961.¹⁰⁴ Fortunately, the reviewer at the FDA to whom Merrell's thalidomide application had been assigned, Dr. Frances Kelsey, had suspicions about the effects of the drug, and ultimately rejected Merrell's application six times, each time demanding more information on the safety of thalidomide.¹⁰⁵ In March of 1962,

96. STEPHENS & BRYNNER, *supra* note 95, at 13-16; McGrath, *supra* note 1, at 606; Pirt, *supra* note 84, at 260.

97. STEPHENS & BRYNNER, *supra* note 95, at 22; McGrath, *supra* note 1, at 607; Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts*, 43 HASTINGS L.J. 301, 313 (1992).

98. Pirt, *supra* note 84, at 261; Sanders, *supra* note 97, at 313. Phocomelia is a serious birth defect that results in severely shortened arms and legs and flipper-like hands and feet. McGrath, *supra* note 1, at 607; Pirt, *supra* note 84, at 261.

99. STEPHENS & BRYNNER, *supra* note 95, at 27-35. The study indicated that taking just one thalidomide pill during pregnancy was enough to cause damage to the unborn fetus. *Id.* at 35.

100. *Id.* at 17; McGrath, *supra* note 1, at 606.

101. See STEPHENS & BRYNNER, *supra* note 95, at 17, 41; McGrath, *supra* note 1, at 607.

102. STEPHENS & BRYNNER, *supra* note 95, at 42-43; McGrath, *supra* note 1, at 607-08; Sanders, *supra* note 97, at 314.

103. STEPHENS & BRYNNER, *supra* note 95, at 9.

104. *Id.* at 39-42.

105. *Id.* at 44, 48-53; McGrath, *supra* note 1, at 608; Pirt, *supra* note 84, at 260-61; Sanders, *supra* note 97, at 314. Dr. Kelsey was awarded the President's Award for Distinguished Federal

after the publication of Professor Lenz's study linking thalidomide to phocomelia, Merrell withdrew its application for FDA approval.¹⁰⁶

In Congress, Tennessee Senator Carey Estes Kefauver and Arkansas Representative Oren Harris used the public attention created by the thalidomide scandal to promote amendments to the FD&C Act to increase the FDA's authority over the safety and efficacy of drugs in the United States.¹⁰⁷ The Drug Amendments of 1962,¹⁰⁸ also known as the Kefauver-Harris Amendments ("K-H Amendments"), were passed unanimously by Congress and were signed into law by President Kennedy in October of 1962.¹⁰⁹ These amendments prohibit the introduction of any new drug to the market (or into interstate commerce) unless it is shown to be both safe and effective for what it purports to do.¹¹⁰ The amendments effectively required, among other things, that clinical trials be conducted prior to new drug approval, that the results of such trials be included in each new drug application, and that adverse drug reactions be reported to the FDA upon request.¹¹¹

Ironically, a required showing of efficacy would not have prevented thalidomide from being distributed in the United States. The drug had been shown effective to treat morning sickness.¹¹² Thalidomide presented safety risks, not efficacy problems. However, the clinical trial requirements, if instituted before the thalidomide "disaster," might have

Civilian Service by President Kennedy in 1962, for keeping thalidomide off the market in the United States. STEPHENS & BRYNNER, *supra* note 95, at 55; McGrath, *supra* note 1, at 609; Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, FDA CONSUMER, Mar.-Apr. 2001, at 24, 25, available at http://www.fda.gov/fdac/features/2001/201_kelsey.html.

106. STEPHENS & BRYNNER, *supra* note 95, at 53-54; McGrath, *supra* note 1, at 608. Thalidomide was finally approved by the FDA in 1998, for use as treatment of leprosy, and is also used today to treat certain other conditions, including HIV and certain forms of cancer, under a very strict system of precautions and monitoring. STEPHENS & BRYNNER, *supra* note 95, at 155-57, 164; Michael E. Franks et al., *Thalidomide*, 363 LANCET 1802, 1802, 1805-08 (2004) (reviewing multiple medical studies and clinical trials on the use of thalidomide for treatments of various conditions and diseases); Lawrence K. Altman, *Thalidomide's Anti-Cancer Use Supported*, N.Y. TIMES, May 22, 2000, at A15. For an in-depth look at the history of thalidomide, from its discovery to its current status, see generally STEPHENS & BRYNNER, *supra* note 95.

107. HUTT & MERRILL, *supra* note 43, at 452; STEPHENS & BRYNNER, *supra* note 95, at 110.

108. Drug Amendments Act of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C. 351(a)).

109. HILTS, *supra* note 72, at 161; HUTT & MERRILL, *supra* note 43, at 452; STEPHENS & BRYNNER, *supra* note 95, at 109-10.

110. McGrath, *supra* note 1, at 609; Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 185, 192 (1971).

111. See Drug Amendments Act of 1962, sec. 102(c)-(d), 103(a)-(b), §§ 505(d)-(e); McGrath, *supra* note 1, at 609.

112. See *supra* note 97 and accompanying text.

enabled scientists to link the phocomelia to the drug sooner, as the patients given thalidomide would have been followed by researchers.

The K-H Amendments strengthen the FDA's control by allowing the refusal of applications that "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof."¹¹³ When evaluating the drug application, the FDA reviewer may also refuse approval if he finds that "on the basis of the information submitted to him . . . and any other information before him . . ." there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use . . . in the proposed labeling thereof,"¹¹⁴ or if he finds that "such labeling is false or misleading in any particular."¹¹⁵ The K-H Amendments then require that the effectiveness of new drugs be proven in clinical trials, in the definition of what qualifies as "substantial evidence":

[T]he term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use . . . in the labeling or proposed labeling thereof.¹¹⁶

However, after making this sweeping requirement, the Amendments lessen the effect by allowing the Secretary to accept results from a single investigation as substantial evidence of effectiveness:

If the Secretary determines, based on relevant science, that data from

113. 21 U.S.C. § 355(d)(1) (2000). The Amendments allow for exceptions to the rule that no unapproved drug should be introduced into interstate commerce, but ONLY for the investigational use of such drugs. *See id.* § 355(i). As a condition of this exemption, the Secretary may require the drug manufacturer to: submit the results of preclinical testing to justify further testing; obtain signed agreements from physicians (or "investigators") participating in the proposed clinical study that all patients given the drug are under his or her supervision; and maintain and submit to the Secretary the records and data obtained during the investigational study. *Id.* § 355(i)(1). All such exemptions are required by the K-H Amendments to be conditioned on the informed consent of all human participants in the investigational study. *Id.* § 355(i)(4). However, the K-H Amendments do not require that reports on investigatory studies be submitted directly to the Secretary. *Id.* (second sentence).

114. *Id.* § 355(d)(5).

115. *Id.* § 355(d)(7).

116. *Id.* § 355(d) (third sentence).

one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.¹¹⁷

The Secretary is also authorized to withdraw approval of a drug application if it is shown by clinical experience, scientific data or other tests that the drug is unsafe for use under the conditions of use for which it was originally approved, or if a lack of substantial evidence of the drug's efficacy can be shown.¹¹⁸

In evaluating the safety and efficacy of a drug, the Secretary undertakes a balancing approach, weighing the benefits of the drug against the risks shown in the various studies. It is generally accepted that "no drug is perfectly safe."¹¹⁹ The FDA's determination that a drug is safe enough to be approved "does not suggest an absence of risk."¹²⁰ Instead, the designation of a drug as "safe" indicates that the FDA has balanced "the clinical significance and probability of its beneficial effects" against "the likelihood and medical importance of its harmful or undesirable effects" and found that the benefits outweigh the risks.¹²¹ The FDA looks at several factors when considering risks and benefits, including but not limited to: "individual benefits from treatment . . . risks of nontreatment or alternative products . . . the severity of the disease being treated . . . the outcome of the disease if untreated . . . the probability and magnitude of any treatment effect . . . [and other] existing therapeutic options."¹²² The government must also take into consideration that the drug will be used by "physicians of varying skills and abilities, in patients with a multitude of disease processes . . . and in patients incorrectly diagnosed or inadequately tested."¹²³ FDA Commissioner George Larrick also recognized that public sentiment can influence the agency's decision to withdraw a drug's approval.¹²⁴

117. *Id.* (final sentence).

118. *See id.* § 355(e).

119. The FDA recognizes that "it is impossible to identify all safety concerns during clinical trials." U.S. DEP'T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMOLOGIC ASSESSMENT 3 (2005), available at <http://www.fda.gov/Cder/guidance/6359OCC.pdf>.

120. U.S. DEP'T OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DEVELOPMENT AND USE OF RISK MINIMIZATION ACTION PLANS 4 (2005), available at <http://www.fda.gov/cder/guidance/6358fml.pdf>.

121. *Id.*

122. *Id.*

123. HUTT & MERRILL, *supra* note 43, at 523 (quotation omitted).

124. *Id.* at 523-24 ("[O]ver a period of time, the direction of Government's decisions will

The K-H Amendments also added another category of “misbranded” products. Under this addition, manufacturers of prescription drugs must include in their advertisements and “other descriptive printed matter” with respect to the drug any information relating to the side effects, contraindications, and effectiveness of the drug as required by regulations to be issued by the Secretary.¹²⁵ In other words, advertisements must contain information on the risks of the drugs in addition to their benefits. However, this requirement does not apply to printed matter deemed to be “labeling” under the FD&C Act.¹²⁶

F. *The Learned Intermediary Doctrine*

The importance of labeling and advertising requirements is the dissemination of information to two groups. Primarily, this information is directed to physicians who would potentially prescribe the drug in question. Secondly, the information is intended for the general public. Manufacturers aggressively use direct-to-consumer advertising to promote their drugs, encouraging potential patients to request the drug from their physicians.¹²⁷

Physicians are responsible for this information under the learned intermediary doctrine.¹²⁸ By case law, manufacturers are considered to have met their burden to warn about risks so long as they make reasonable efforts to inform the prescribing physicians,¹²⁹ particularly those who are normally expected to use the particular drug,¹³⁰ and they

inevitably be influenced by public reaction. . . . If it should become the overwhelming public view that society should drastically limit the risk no matter how much good a drug can do, then we would be forced to remove from the market many drugs whose good far outweighs their harm.”)

125. See Drug Amendments Act of 1962, Pub. L. No. 87-781, sec. 131(a), § 502, 76 Stat. 780, 791-92 (codified at 21 U.S.C. § 352(n) (2000)).

126. Drug Amendments Act of 1962, sec. 131(a), § 502, 76 Stat. at 792. “Labeling” is defined under the Act as “all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 201(m), 52 Stat. 1040, 1041 (1938) (codified as amended at 21 U.S.C. § 321(m) (2000)).

127. See Marvin M. Lipman, *Bias in Direct-to-Consumer Advertising and Its Effect on Drug Safety*, 35 HOFSTRA L. REV. 761, 764 (2006). For a general discussion of problems with the pharmaceutical industry’s use of direct-to-consumer advertising, see generally *id.*

128. This doctrine protects manufacturers of prescription drugs and devices in that it holds physicians responsible for providing product information to the ultimate consumer—the patient. HUTT & MERRILL, *supra* note 43, at 422; Maxwell J. Mehlman, *Off-Label Prescribing* (May 2005), http://www.thedoctorwillseeyounow.com/articles/bioethics/offlabel_11/#ref2.

129. See *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978, 991, 993 (8th Cir. 1969) (affirming the trial court’s ruling, finding a drug manufacturer liable because its sales force did not adequately warn the physicians).

130. *Magee v. Wyeth Labs., Inc.*, 29 Cal. Rptr. 322, 327-28 (Ct. App. 1963).

are not required to warn the public.¹³¹ While advertising may be primarily directed to the ultimate consumer of the drug—the patient—labeling is intended to inform the physician of the (approved) uses of the drug, along with risks and benefits of use, and any contraindications that might preclude the use of the drug. The chemical and biochemical nature of drugs and their effects on the body is further explained in the “package inserts” of the drug, and while provided to the patient, is very complex and generally requires advanced medical knowledge. Patients, therefore, rely on their physicians to know and understand the workings and uses of various drugs, and to prescribe them in the best interest of the patient. If this information is not provided to the physicians by the manufacturer, or by other means,¹³² the physician cannot use it in his or her decision on patient treatment.

III. THE REFLECTION OF A DIFFERENCE OF SCIENTIFIC OR MEDICAL OPINION AND OTHER LABELING REQUIREMENTS

A. Case Study: *Bradley v. Weinberger*

In 1973, in *Bradley v. Weinberger*,¹³³ the FDA chose to enforce disclosure of an allegedly increased risk of cardiovascular deaths related to the use of certain drugs.¹³⁴ The drugs in question were oral hypoglycemic agents, used to control diabetes by lowering the patient’s blood sugar level.¹³⁵ After one federally funded study concluded that hypoglycemic agents had no significant effect on prolonging life, but that their use might increase the risk of death in comparison to other treatments, the FDA proposed a labeling change on all such drugs

131. *Stottlemire v. Cawood*, 213 F. Supp. 897, 899 (D.D.C. 1963). However, manufacturers have been required to warn the public of the risks associated with use of birth control pills:

Oral contraceptives . . . bear peculiar characteristics which warrant the imposition of a common law duty on the manufacturer to warn users directly of associated risks. Whereas a patient’s involvement in decision making concerning use of a prescription drug necessary to treat a malady is typically minimal or nonexistent, the healthy, young consumer of oral contraceptives is usually actively involved in the decision to use “the pill,” as opposed to other available birth control products, and the prescribing physician is relegated to a relatively passive role.

MacDonald v. Ortho Pharm. Corp., 475 N.E.2d 65, 69 (Mass. 1985).

132. Physicians often look to clinical studies and reports in peer-reviewed journals, in addition to the information provided by the drug manufacturer. See Daniel B. Klein & Alexander Tabarrok, *Who Certifies Off-Label?*, 27 REGULATION 60, 61 (2004).

133. 483 F.2d 410 (1st Cir. 1973).

134. *Id.* at 411-12.

135. *Id.* at 411.

reflecting this danger.¹³⁶ Although the plaintiffs, a group of physicians and one diabetes patient, were granted a preliminary injunction by the district court of Massachusetts, preventing the enforcement of the labeling change, the First Circuit vacated the injunction (though on procedural grounds rather than on the merits of the claim).¹³⁷

1. Factual Background

The study at issue in this case was performed by the University Group Diabetes Program (“UGDP”) to evaluate the long-term effects of oral hypoglycemic agents in treatment regimens of patients with adult-onset diabetes.¹³⁸ The study involved the following treatment groups: diet control, diet plus regular insulin doses, diet plus varying insulin doses, and diet plus fixed doses of the oral hypoglycemic agents tolbutamide or phenformin hydrochloride.¹³⁹ The federally funded study was coordinated at the University of Maryland, involved twelve clinics nationwide and monitored approximately 1,200 diabetic patients for a five to eight year period of treatment.¹⁴⁰ In 1970, the UGDP announced that the initial results of the study indicated that treatment with tolbutamide resulted in higher risk of death from cardiovascular disease than with the other treatments studied, and the UGDP later announced similar findings related to the use of phenformin hydrochloride.¹⁴¹ In response to criticism and publicity surrounding these results, the FDA convened an “ad hoc committee of experts” and decided it would require labeling changes to reflect the cardiovascular risks of all oral hypoglycemic agents.¹⁴²

The Committee on the Care of the Diabetic (“CCD”), a “national association of physicians [and experts] involved in the [care and] treatment of diabetes . . . patients,” was very critical of the UGDP

136. *Id.* at 411-12.

137. *Id.* at 411, 417.

138. *Id.* at 411; *see also* *Forsham v. Harris*, 445 U.S. 169, 171 (1980). For the connection between *Forsham* and *Bradley*, *see infra* notes 144, 150 and accompanying text. The initial results of the UGDP study were published in Martin G. Goldner et al., *Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes*, 218 JAMA 1400 (1971).

139. Goldner et al., *supra* note 138, at 1401. The Court in *Forsham* indicates that these two oral hypoglycemic drugs were studied as separate treatment regimens, *Forsham*, 445 U.S. at 171, while the *Bradley* court seems to combine these into one treatment group, *Bradley*, 483 F.2d at 411-12. The actual study indicates that the “fifth” treatment group of phenformin was added to the study eighteen months after patient recruitment began for the initial four group study. Goldner et al., *supra* note 138, at 1401.

140. *Forsham*, 445 U.S. at 171-72; *Bradley*, 483 F.2d at 411.

141. *Forsham*, 445 U.S. at 172. For the initial results of the tolbutamide study, *see generally* Goldner et al., *supra* note 138.

142. *Bradley*, 483 F.2d at 412.

study.¹⁴³ Concerned largely with the patient selection controls and the use of fixed doses of the oral hypoglycemic agents in the study as opposed to variable doses as used in general medicinal practice, the CCD requested access to the UGDP raw data, in order to conduct its own review of the findings.¹⁴⁴ The CCD also responded to the FDA's decision to change the labeling requirements of oral hypoglycemic agents, sending a petition in October 1971, requesting that the FDA withdraw its labeling recommendation; provide the CCD with the raw data of the UGDP study; include references to the claimed deficiencies of the UGDP study whenever the FDA commented on it; and "in accord with [the FDA's] policy of fair balance, disseminate with equal emphasis and frequency studies and individual expert opinions differing with the [UGDP] study."¹⁴⁵ The CCD included with the petition more than 200 pages of scientific studies, papers and comments supporting the position that there were no significant cardiovascular risks from oral agents, and supplemented this with additional material three months later.¹⁴⁶

Nevertheless, in May 1972, the FDA published the "Final Labeling Approved for Oral Hypoglycemic Drugs," adding a special warning section to the drug label and proposing changes in the "indications" section.¹⁴⁷ In June of that year, the Commissioner formally responded to the CCD petition, criticizing the contrary studies and providing one hundred pages of materials from scientific studies and comments of major medical groups that supported the position adopted by the FDA.¹⁴⁸ The CCD replied with a letter suggesting that the proposed label constituted a "misbranding" under federal statutes and FDA regulations, suggesting that the package insert of these drugs include a reflection of the difference in medical and scientific opinion of the cardiovascular

143. *Forsham*, 445 U.S. at 172; *Bradley*, 483 F.2d at 412.

144. *Forsham*, 445 U.S. at 172; *Bradley*, 483 F.2d at 412. This request was denied, and the CCD then tried to gain access to the raw data via a Freedom of Information Act ("FOIA") request to the Secretary of Health, Education and Welfare ("HEW"). *Forsham*, 445 U.S. at 171, 176. When this request was also denied, CCD filed suit in the United States District Court for the District of Columbia to require HEW to release the information, claiming that since the UGDP study was funded by federal grants, all study results were "owned" by the federal government and subject to such a request. *Id.* The district court granted summary judgment for HEW, claiming that the raw data "did not constitute 'agency records' under the FOIA." *Id.* at 176. The Court of Appeals confirmed on the same reasoning. *Forsham v. Califano*, 587 F.2d 1128, 1133, 1135 (D.C. Cir. 1978). The Supreme Court granted certiorari and affirmed that the data sought by CCD are not "agency records." *Forsham*, 445 U.S. at 186-87.

145. *Bradley*, 483 F.2d at 412.

146. *Id.*

147. *Id.*

148. *Id.*

risk, and again requesting the patient records from the UGDP study.¹⁴⁹ The Commissioner again denied the CCD's requests, stated that his decisions constituted "final agency action," and the CCD turned to the courts.¹⁵⁰ The plaintiffs' claims in *Bradley v. Weinberger* were based on the misbranding statutes and regulations.¹⁵¹

2. District Court Actions and Arguments

The plaintiffs in *Bradley* filed suit in the District Court for the District of Massachusetts on August 11, 1972, and the court issued a temporary restraining order the same day to prevent the FDA from enforcing the labeling change and to prevent the pharmaceutical companies from complying with the proposed change.¹⁵² Less than three weeks later, an emergency district judge denied the preliminary injunction, finding that the plaintiffs had not "demonstrated 'a reasonable probability' of showing that the FDA's decision . . . was arbitrary or capricious," and that the "irreparable injury" that the plaintiffs might suffer as a result of the FDA's actions did not outweigh the injury that might result to the general public if the labeling changes were not made.¹⁵³ The plaintiffs brought a second motion for preliminary injunction in September 1972, which was denied (this time by the judge who had received the case as a permanent assignment) because no changes had been made to the complaint and no new evidence had been presented to support the motion.¹⁵⁴ On October 17, 1972, the plaintiffs filed a motion for leave to amend their complaint, along with new motions for a temporary restraining order and a preliminary injunction.¹⁵⁵ The amended complaint alleged that the proposed label was in violation of federal statute and the FDA's governing regulations, because it was itself misleading and, if put into effect, would render the drug to be misbranded.¹⁵⁶

The statutes relied on by the plaintiffs are found in the codification of the Federal Food, Drug and Cosmetic Act of 1938 and its subsequent

149. *Id.* at 412-13.

150. *Id.* at 413. The CCD tried to get the study results via the *Forsham* cases, discussed *supra* note 144. Several of the physician plaintiffs in *Bradley* were CCD members. *Bradley*, 483 F.2d at 412.

151. *See infra* notes 156-62 and accompanying text.

152. *Bradley*, 483 F.2d at 411, 413.

153. *Id.* at 413.

154. *Id.*

155. *Id.*

156. *Id.*

amendments.¹⁵⁷ The first statute states, in relevant part, “A drug . . . shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular.”¹⁵⁸ Such misbranding can result in the withdrawal of the drug application approval.¹⁵⁹ The second statute comes from the definitions section of the Act and deals with determining whether or not a label is misleading. It reads:

If an article is alleged to be misbranded because the labeling . . . is misleading, then in determining whether the labeling . . . is misleading there shall be taken into account (among other things) not only representations made or suggested . . . but also the extent to which the labeling . . . *fails to reveal* facts material in the light of such representations or material with respect to consequences which may result from the use of the articles to which the labeling . . . relates¹⁶⁰

At the time, the FDA regulation implementing this statute took into consideration a difference of scientific opinion and was the primary basis of the plaintiffs’ claims. This regulation, 21 C.F.R. § 1.3 (1973), read:

The existence of a difference of opinion, among experts qualified by scientific training and experience, as to the truth of a representation made or suggested in the labeling is a fact (among other facts) the failure to reveal which may render the labeling misleading, if there is a material weight of opinion contrary to such representation.¹⁶¹

Plaintiffs’ argument, essentially, was that the proposed FDA label for oral hypoglycemic agents, by failing to account or reference the difference of opinion in regards to the cardiovascular risks, rendered the label misleading.¹⁶²

In originally addressing the CCD claims, before this action was taken to the federal courts, the Food and Drug Commissioner rejected the argument that a balance on the label was needed regarding the potential increased cardiovascular risk, relying on Congress’s determination in the 1962 amendments to the Food, Drug and Cosmetic Act that “unsubstantiated expert opinion could no longer suffice to

157. See 21 U.S.C. §§ 301-397 (2000).

158. *Id.* § 352(a).

159. See *id.* § 355(e).

160. *Id.* § 321(n) (emphasis added); see also *Bradley*, 483 F.2d at 416.

161. *Bradley*, 483 F.2d at 416 (citing 21 C.F.R. § 1.3 (1973) (amended 1976)). Note that this regulation has since been changed. For the current regulation, see *infra* notes 185-86 and accompanying text.

162. *Bradley*, 483 F.2d at 416.

establish the effectiveness of drugs.”¹⁶³ In order to include the difference of opinion on the label or in the package insert, the Commissioner felt that the plaintiffs needed to provide “substantial evidence” of their claims, and relied on the statute’s definition of “substantial evidence” as “adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”¹⁶⁴ The Commissioner determined that the studies and comments submitted by the CCD with their initial petition to the FDA did not meet the statutory standard of “substantial evidence.”¹⁶⁵

The District Court received and reviewed affidavits from plaintiffs and defendants, and heard oral arguments from both sides.¹⁶⁶ On November 3, 1972, the plaintiffs’ motions to amend the complaint and for a preliminary injunction were granted.¹⁶⁷ The court found that plaintiffs had shown a “reasonable likelihood upon a full hearing on the merits [that] they would be successful in establishing [that] the defendants . . . have not . . . complied with 21 C.F.R. § 1.3; 21 U.S.C. § 321(n) and 21 U.S.C. § 352(a)” and that the harm to the plaintiffs would likely be greater than harm to the defendants absent such relief.¹⁶⁸ When these statutory compliance arguments were reviewed on appeal, the First Circuit did not make a determination on the merits, but due to procedural errors sent the issue back to the Commissioner for further review.¹⁶⁹

3. First Circuit Appeal

While the First Circuit acknowledged that the district court had jurisdiction to review the FDA’s decision, as it was “final agency action for which there is no other adequate remedy in a court,”¹⁷⁰ it ultimately concluded that the district court had improperly considered the affidavits of both sides in making its determination,¹⁷¹ rather than looking solely to the “administrative record that was before the [Commissioner] at the time he made his decision.”¹⁷² The claim made by plaintiffs to the

163. *Id.*

164. 21 U.S.C. § 355(d) (2000); *Bradley*, 483 F.2d at 415.

165. *Bradley*, 483 F.2d at 416.

166. *Id.* at 413.

167. *Id.*

168. *Id.*

169. *Id.* at 417.

170. 5 U.S.C. § 704 (2000); *Bradley*, 483 F.2d at 413.

171. *Bradley*, 483 F.2d at 414, 417.

172. *Overton Park, Inc. v. Volpe*, 401 U.S. 402, 420 (1971).

district court, that the proposed label change would itself be “misbranding” according to the FDA’s own regulations, was never brought before the Commissioner and was not referred to in the administrative record.¹⁷³ The Commissioner had only addressed the argument that a fair balance to both opinions should be provided on the label.¹⁷⁴ Because the Commissioner did not consider the “meaning of this [misbranding] regulation, its relationship to the substantial evidence test, the intersection of the safety, effectiveness, and misbranding requirements, or the applicability of the misbranding requirements, both statutory and regulatory, to an FDA proposal for re-labeling,”¹⁷⁵ and due to the novelty of the situation where the misbranding statutes and regulations were “sought to be applied not to the manufacturer’s label but to the FDA’s proposal for alteration of the label in light of new information,”¹⁷⁶ the First Circuit remanded this case for further administrative proceedings within the FDA.¹⁷⁷

The court reasoned that plaintiffs had not exhausted their administrative remedies, since they had not presented all relevant issues to the administrative body, and so the district court should not have entertained the suit.¹⁷⁸ Additionally, as a result of the plaintiffs’ failure to exhaust their administrative remedies, the district court did not, and could not, rely solely on the administrative record in its decision, and so erred in granting the preliminary injunction.¹⁷⁹

4. Discussion

The First Circuit made special note in its decision that “extensive negotiations between the parties to arrive at a mutually acceptable solution to the labeling problem had been carried on during much of this litigation.”¹⁸⁰ It then remanded the case to the FDA with the “pious hope” that continued negotiations would “produce the most informed and responsible solution possible.”¹⁸¹ These statements by the court support the inference that the court did not want to get involved on the merits of the case. It is hard to blame the court for having this opinion. This case was unprecedented in that it was not the pharmaceutical

173. *Bradley*, 483 F.2d at 415.

174. *Id.* at 416.

175. *Id.*

176. *Id.* at 415.

177. *Id.* at 417.

178. *Id.*

179. *Id.*

180. *Id.*

181. *Id.*

manufacturers that were resisting the negative change to the labeling, but the prescribing physicians and many experts in the field.¹⁸² The drugs in question were, at that time, the primary drugs used to aid in the treatment of Type II Diabetes.¹⁸³

When comparing the facts of *Bradley* to the factual background of the Vioxx “difference of opinion,” it is difficult to understand why the FDA did not take a similar “err on the side of caution” approach. In fact, one could argue that the FDA had even *more* reason to be cautious of Vioxx once given the studies indicating greater risk of heart attacks and strokes. Arthritis sufferers had other medications available, both prescription and over-the-counter NSAIDs, that worked to relieve the pain of inflammation. In contrast, Type II diabetics, at the time of *Bradley*, had no other effective options.¹⁸⁴

B. Labeling Requirements and Regulations After Bradley

After the decision in *Bradley*, the FDA changed the governing regulations to reflect the requirement of substantial evidence in support of any difference of opinion regarding drug labeling.¹⁸⁵ The current regulation reads, in relevant part:

(a) Labeling of a food, drug, device, or cosmetic shall be deemed to be misleading if it fails to reveal facts that are:

- (1) Material in light of other representations made or suggested . . .
- (2) Material with respect to consequences which may result from use of the article under: (i) The conditions prescribed in such labeling or (ii) such conditions of use as are customary or usual.

. . . .

(c) Paragraph (a) of this section does not:

- (1) Permit a statement of differences of opinion with respect to warnings (including contraindications, precautions, adverse reactions,

182. *Id.* at 415.

183. Alexander Tal, *Oral Hypoglycemic Agents in the Treatment of Type II Diabetes*, 48 AM. FAM. PHYSICIAN 1089, 1089, 1092-93 (1993), available at http://findarticles.com/p/articles/mi_m3225/is_n6_v48/ai_14658181/print. Insulin is the primary drug to aid in treatment of Type I, or insulin-dependent, diabetes, and is now generally used to treat Type II diabetes only when oral medication has become ineffective. *Id.*; see also Hanna Lubbos et al., *Oral Hypoglycemic Agents in Type II Diabetes Mellitus*, 52 AM. FAM. PHYSICIAN 2075 (1995), available at http://findarticles.com/p/articles/mi_m3225/is_n7_v52/ai_17776044/print. “Second-generation” oral hypoglycemic drugs have been developed to treat Type II diabetes with fewer negative side effects than the “first-generation” drugs at issue in this case. Lubbos et al., *supra*.

184. See *supra* note 183.

185. 42 Fed. Reg. 15,553, 15,555 (Mar. 22, 1977) (codified at 21 C.F.R. § 1.21 (2007)).

and other information relating to possible product hazards) required in labeling for food, drugs, devices, or cosmetics under the act.

(2) Permit a statement of differences of opinion with respect to the effectiveness of a drug unless each of the opinions expressed is supported by substantial evidence of effectiveness as defined in sections 505(d) and 512(d) of the act.¹⁸⁶

Other significant changes in labeling regulations have occurred in the year or two preceding the date of this Note. In 2005, the FDA began requiring pharmaceutical manufacturers to submit drug labeling information in an electronic format. These submissions are being compiled into an online clearinghouse in order to provide the most up-to-date information to *all* members of the public (physicians, patients and other healthcare information providers) via the Internet.¹⁸⁷ In January of 2006, the FDA announced revisions to the formatting requirements of package inserts of prescription drugs, in order to make the most important information easier to find and understand.¹⁸⁸

IV. POLICY DISCUSSION

A. *Difference of Opinion in Case Law and Legislative History*

In terms of disease treatment and pharmaceutical drug regulation, differences of opinion are not a new phenomenon. As early as 1902, the United States Supreme Court “questioned the [federal] government’s authority to regulate the truth of therapeutic claims.”¹⁸⁹ In *American School of Magnetic Healing v. McAnnulty*, the Court stated:

As the effectiveness of almost any particular method of treatment of disease is, to a more or less extent, a fruitful source of difference of opinion, even though the great majority may be of one way of thinking, the efficacy of any special method is certainly not a matter for the decision of [the government official] . . . [u]nless the question may be reduced to one of fact as distinguished from mere

186. 21 C.F.R. § 1.21(a), (c) (2007).

187. See *The FDA Announces New Prescription Drug Information Format*, FDA CONSUMER, Mar.-Apr. 2006, at 25, 26-27; see also Press Release, U.S. Food & Drug Admin., FDA Announces New Prescription Drug Information Format To Improve Patient Safety (Jan. 18, 2006), available at <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01272.html> [hereinafter Press Release, FDA Announces].

188. Press Release, FDA Announces, *supra* note 187; see Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601).

189. HUTT & MERRILL, *supra* note 43, at 389.

opinion¹⁹⁰

In 1916, the Supreme Court expounded on the policy regarding differences of opinion in regards to the labeling of drug products. In *Seven Cases of Eckman's Alterative v. United States*,¹⁹¹ the plaintiff challenged the section of the Food & Drugs Act of 1906 that deemed a drug to be misbranded: “[i]f its package or label shall bear or contain any statement . . . regarding the curative or therapeutic effect of such article . . . which is false and fraudulent.”¹⁹² Plaintiffs argued that the determination of a false and fraudulent statement under this statute entered the “domain of speculation” by the government that had been prohibited by *Magnetic Healing v. McAnnulty*.¹⁹³ The Court responded by declaring that, in enacting the challenged statute, “Congress deliberately excluded the field where there are honest differences of opinion between schools and practitioners,”¹⁹⁴ and intended the statute to apply when the misbranding was included with the goods “with actual intent to deceive,” rather than an honest belief of the statement.¹⁹⁵ The Court believed, however, that in the type of situation presented in this case, “Congress recognized that there was a wide field in which assertions as to curative effect are in no sense honest expressions of opinion but constitute absolute falsehoods,”¹⁹⁶ and therefore upheld the validity of the statute.¹⁹⁷

When discussing the proposed Kefauver-Harris Amendments, Congress gave specific consideration to a difference of opinion regarding the proof of efficacy to be required by the Amendments. The Senate report contains the following:

When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted even though there may be preponderant evidence to the contrary based upon equally reliable studies. . . . What the committee intends is to permit the claim for this new drug to be made to the medical profession with a proper explanation of the basis on which it

190. 187 U.S. 94, 105-06 (1902).

191. 239 U.S. 510 (1916).

192. *Id.* at 512-13 (citing Food & Drug Act of 1906, Pub. L. No. 59-384, § 8, 34 Stat. 768, 770, amended by Act of Aug. 23, 1912, Pub. L. No. 62-301, 37 Stat. 416).

193. *Eckman's Alterative*, 239 U.S. at 517.

194. *Id.*

195. *Id.*

196. *Id.* at 518.

197. *Id.*

rests.¹⁹⁸

This seems to allow for the approval of a drug whose safety and/or efficacy is effectively disproved by a credible study, as long as a study purported to prove the safety and efficacy is submitted with “a proper explanation.” Under this type of argument, differences of opinion would always be resolved in favor of drug approval.

The last sentence of this statement indicates that Congress expected conflicting claims to be made available, with background and supporting materials, to “the medical profession,” or in other words, to the prescribing physicians. This is congruous with the learned intermediary doctrine that requires manufacturers to adequately warn and inform physicians.¹⁹⁹ Under this combined interpretation of the Senate report, applications for the approval of drugs could be supported with claims of safety and efficacy that are the subject of a difference of opinion among medical and scientific experts. The FDA would favor drug approval, and physicians would bear the burden of sorting through the myriad of contrary claims to determine whether or not the drug should be prescribed to their patients.

Bradley v. Weinberger provides a specific example of how the FDA balanced a difference of opinion. Although the legislation and regulations were somewhat ambiguous, the court ultimately left the resolution to the FDA.²⁰⁰ Post-*Bradley*, the regulations were changed to reflect the FDA’s decision in the case.²⁰¹ In this respect, the regulation on noting differences of opinions with respect to warnings required in labeling,²⁰² promulgated after *Bradley*, is a mixed blessing. In cases like *Bradley*, where the FDA included a suspected risk in the labeling,²⁰³ this regulation serves to err on the side of caution, informing the public of the possible danger even if the study suggesting the danger is alleged to be flawed or misinterpreted. In the Vioxx case, however, the policy behind this regulation may have served to keep consumers uninformed. In evaluating the results of the Naproxen study, the FDA was willing to accept Merck’s interpretation that the study showed the extra-beneficial aspects of Naproxen, and in this determination effectively ignored the

198. S. REP. NO. 87-1744, at 16 (1962), as reprinted in 1962 U.S.C.C.A.N. 2884, 2892.

199. See *supra* Part II.F.

200. *Bradley v. Weinberger*, 483 F.2d 410, 417 (1st Cir. 1973).

201. See *supra* note 185-86 and accompanying text.

202. 21 C.F.R. § 1.21(c) (2007).

203. *Bradley*, 483 F.2d at 412.

interpretation that the study showed the increased risks presented by rofecoxib.²⁰⁴

In relation to other cases mentioned in the introduction—is there a pattern that results when the decision on labeling (when a difference of opinion exists) is made by the FDA and the drug sponsor (as in the Vioxx case) as opposed to being made by the FDA, an “independent” study group and practicing physicians (as in *Bradley*)?

B. Policy Stakeholders and Why the Individual Should Win

In the world of pharmaceutical development, there are many entities (or stakeholders) whose interests are at stake with each FDA drug application. The manufacturer’s interest is primarily commercial—can it sell the drug, maximize its market share, and therefore maximize its profit? Academia’s interest was originally in the scientific evaluation of drug studies and clinical trials—is the data accurate and is the analysis “good”? Is the world of scientific and medical knowledge being expanded? However, today, university-conducted clinical trials are largely funded by the pharmaceutical manufacturers, shifting control of these studies to the commercial sector.²⁰⁵ The government has a security interest in pharmacology—with the threat of bio-terrorism on the horizon, do we, as a country, have the knowledge and resources to survive? The regulators (most notably the FDA) are interested in promoting the safety, efficacy, and quality of the drugs available on the market. Their interest is in the public health of society as a whole, and as a part of society, the health of patients who will ultimately take the drugs. However, since the enactment of the Prescription Drug User Fee Act of 1992 (and its subsequent renewals), the pharmaceutical industry provides between twenty to fifty percent of the funding for the FDA’s activities.²⁰⁶ The regulating agency is therefore dependent on those it is supposed to be regulating. Physicians who prescribe and recommend medications and treatments are interested in the health of their patients and in practicing good medicine. Part of that practice is being knowledgeable about the risks and benefits of each drug or treatment they recommend—they want to have this information made available to them so they can use it in treatment decisions.

204. See *supra* notes 20-25 and accompanying text.

205. Abramson, *supra* note 9, at 698.

206. See Merrill Goozner, *Conflicts of Interest in the Drug Industry’s Relationship with the Government*, 35 HOFSTRA L. REV. 737, 739 (2006); Maurice Hinchey, *The Fight to Safeguard American Drug Safety in the Twenty-First Century*, 35 HOFSTRA L. REV. 685, 687 (2006).

Finally, and possibly most importantly, patients have an interest in feeling better. They want the drug or treatment to work—to cure the ailment that it is said it will cure. For some, medicines will treat an isolated complaint and return the patient to a normal and healthy life. For others, medicines will be used to control severe disabilities or disorders, and to provide the best life possible for that patient. When balancing positive and negative effects of each drug, the patient has an interest in learning about those effects through individual research and via discussion with his or her physician.

Intertwined with the considerations of each stakeholder is the idea of empowerment. Society is empowered when good drugs (i.e., safe and effective drugs) are made available to all the people who need them, and when treatments are discovered for severe, debilitating, and fatal conditions. The commercial sector is empowered when it can produce a drug at minimal cost, then turn around and sell it to maximize profit. The individual is empowered when he or she has the resources available to make an informed decision about his or her own treatment. When the FDA creates policy controlling approval of drugs based on safety and efficacy, it is caught in a battle between these empowered “classes.” The FDA (and the government through the FDA) wants to promote the research of new drugs to treat an ever-expanding library of diseases and conditions, wants to increase the availability of life-saving and “life-improving” drugs, and wants to make sure that the drugs are safe for human use. These desires relate, respectively, to the commercial, societal, and individual empowerment goals of the FDA. However, recent events concerning the harmful effects of “approved” drugs, and the significant time delay in the availability of risk information (allowing manufacturers to rake in profits for as long as possible) indicate that the commercial sector is winning this particular three-way tug of war.²⁰⁷ The FDA needs to rebalance its efforts, remembering that the issues at stake in its approval and labeling decisions are the lives and health of American citizens, so commercial interests must yield to individual and societal empowerment.

V. HOW DIFFERENCES OF OPINION SHOULD BE HANDLED

As previously stated, the federal drug policy seems to currently favor the commercial pharmaceutical industry. Differences of opinion regarding drug safety and efficacy in a new drug application seem to be decided in favor of the manufacturer (at least initially). After approval,

207. See Hinchey, *supra* note 206, at 686-90.

challenges to a drug's safety or to the adequateness of the drug's label regarding risks are seemingly set aside until the effects of the risks become so egregious that the manufacturer or the FDA is forced to address them. This set-aside period allows the manufacturer to maximize profits before removing either an indication for a drug or the drug itself. In order to shift the focus of federal drug policy in the United States back to where it should be, protection of the individual consumer and the protection of societal well-being from adulterated or misbranded drugs, the legislation and regulations should be changed in two ways.

First, when faced with a difference in scientific or medical opinion, whether on a study's interpretation or on the reliability of any given study, the stated policy should mandate that the FDA (and consequently the manufacturer) err on the side of caution. The consumer will benefit more from a label that includes as a potential side effect an "increased risk of heart attack" (as in the case of rofecoxib)²⁰⁸ than a label that does not indicate an adverse effect simply because the manufacturer is able to explain away the negative implications of a clinical study. The inclusive label will allow for increased communication between the consumer and his or her prescribing physician. The consumer and physician can research and discuss the "potential" risks, and the consumer can then make the ultimate decision as to whether or not the expected benefits of that treatment outweigh the potential risks. Because it is the consumer whose life and body is at stake in this decision, the consumer should have the final say.²⁰⁹

Secondly, the statutes and regulations should continue to take advantage of the electronic information age. Broad steps have been taken in the right direction with the FDA regulation requiring electronic submission of prescribing information,²¹⁰ the creation of an online information clearinghouse,²¹¹ broadened disclosure of clinical trial information,²¹² and Congressional proposals both to require the registration of all clinical trials and the posting of all results in a central database, and to enhance criminal penalties for concealing evidence of

208. See *supra* note 21 and accompanying text.

209. Please note, however, that I am not here proposing that the FDA never make determinations on drug safety over the choice of the consumer. The FDA should still control the approval of drug applications based on proved safety and efficacy of the drug, and the withdrawal of such approval when the overall risks of the drug are shown to outweigh the beneficial aspects.

210. See *The FDA Announces New Prescription Drug Information Format*, *supra* note 187, at 26-27.

211. *Id.* at 25-27.

212. See Scheineson & Sykes, *supra* note 31, at 528-29, 531-35, 539-43.

serious adverse drug reactions.²¹³ The online clearinghouse can be further developed to allow for the disclosure of differences of opinion in the following way:

(1) When the FDA is faced with a report such as the naproxen/rofecoxib study, it can follow its current guidelines requiring that substantial evidence exist to support the various interpretations.²¹⁴

(2) Regardless of which interpretation the FDA ultimately supports, the proponents of the other interpretation should file for recognition of a Difference of Opinion (“DOP”).

(3) The FDA should then review this DOP application, using a *lower* burden than that of “substantial evidence.”²¹⁵ In defining this lower burden, the FDA should fashion a rule that recognizes a scientifically sound theory (although not supported to the extent of “substantial evidence”) but that dismisses unsubstantiated or tenuous claims.

(4) If the contrary opinion is supported under the lower burden, the label and package insert of the drug in question should be marked in some recognizable way to draw the attention of both physicians and consumers.

(5) Details and support of the contrary opinion should then be submitted to the FDA in electronic format.

(6) On the online clearinghouse, the drug information should include the DOP marking and a link should be provided to the contrary opinion and its supporting materials.²¹⁶

VI. CONCLUSION

Under the DOP policy described above, the “scandal” aspect of the Vioxx case would, theoretically, have been averted. When the FDA was notified of the naproxen study and made its decision to accept Merck’s explanation, Eric Topol’s group could have filed an application for a DOP.²¹⁷ Upon presenting their interpretation of the study, the FDA

213. *See id.* at 535-39.

214. *See supra* note 186 and accompanying text.

215. A lower burden than substantial evidence is required by this proposal, as the Commissioner would theoretically already have ruled that “substantial evidence” does NOT exist (otherwise it would require a balanced label under the current regulation).

216. Note that this proposal is equally applicable when the contrary opinion promotes negative connotations to the drug, as in the Vioxx scandal, and when the contrary opinion ascribes positive implications, as in *Bradley*.

217. The Topol study can be compared to the UGDP study in *Bradley*. It looked at the VIGOR study and combined it with the results of its own study to make the claim that rofecoxib had a negative side effect of increased risk of heart attack (when compared to other alternative drugs).

would have recognized this difference of opinion by marking the prescription information and labeling of Vioxx. Physicians, when prescribing Vioxx, and consumers, when researching or taking Vioxx, would then have seen this marking, and would have accessed the online information clearinghouse. Through this location, the physician and consumer would have been able to learn about and discuss the difference of opinion in more detail. Ultimately, the *consumer*, guided by his or her physician, would have made an informed choice as to whether or not to take the medicine.²¹⁸

Combined with requirements that mandate disclosure of adverse reactions and effects, the information superhighway can quickly update drug information, so that the individual may maintain control.²¹⁹ Consumers today are largely internet savvy, as evidenced by the success of eBay, Amazon.com, and infinite other online stores. In the health care field, patients actively research diagnoses, diseases, complaints and ailments, often without any physician input.²²⁰ For example, WebMD is a very popular health care information site. In this regard, consumers are slowly eclipsing the environment that fostered the learned intermediary doctrine. With increased avenues of public access to information, patients do not always need to rely so heavily on their physicians. However, since much of the pharmaceutical information is still very technical, it is unlikely that the doctrine will be overturned. Unless the researchers and manufacturers make all information on risks and benefits of pharmaceutical drugs available, it does not matter whether the physicians or the patients are held responsible for researching drug indications and effects. On the other hand, if more information is made available, a higher quality of discussion and individual risk/benefit balancing can be had between a patient and his or her physician.

It has long been accepted in the United States that “[e]very human being of adult years and sound mind has a right to determine what shall

Unfortunately, unlike its decision in *Bradley*, the FDA did not err on the side of caution, and did not mandate or propose a label change for several years.

218. Similarly, the plaintiff physicians in *Bradley* could have filed for a DOP application under this proposal, thus informing the public of the wealth of opinion denying increased risks.

219. The High-Performance Computing Act of 1991 was a significant push in the development of what is now “the Internet.” See High-Performance Computing Act of 1991, Pub. L. No. 102-194, 105 Stat. 1594 (1991) (codified as amended at 15 U.S.C. § 5501 (2000)). A proposed amendment to this Act in 1993 specifically identified health care as a field that would benefit from the advanced technology of a coordinated high-performance and high-speed computer network. See National Information Infrastructure Act of 1993, H.R. 1757, 103d Cong. § 2(3) (1993).

220. And often to the disgruntlement of physicians, who have to work with, or work around, a “self-diagnosed” patient.

be done with his own body.”²²¹ A patient has the right to refuse life-sustaining treatments.²²² A patient has the right to choose whether or not to participate in a medical research study.²²³ It is time that patients have the appropriate resources and power to choose what drugs they are willing to put into their own bodies. Increased transparency and disclosure from the pharmaceutical and pharmaceutical research industries will allow patients and prescribing physicians to access the full breadth of information available on these drugs, and to evaluate the risk/benefit ratio for each individual patient—allowing the patient to make the ultimate choice.

*Karen Baswell**

221. *Schloendorff v. Soc’y of N.Y. Hosp.*, 105 N.E. 92, 93 (N.Y. 1914), *overruled on other grounds by Bing v. Thunig*, 143 N.E.2d 3, 9 (N.Y. 1957).

222. *See In re A.C.*, 573 A.2d 1235, 1243-44, 1247 (D.C. 1990).

223. *See Moore v. Regents of Univ. of Cal.*, 793 P.2d 479, 484-85 (Cal. 1990).

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