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Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion

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Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion

Katherine A. Helm*

INTRODUCTION: SETTING THE STAGE	118
I. THE FDA'S ASCENSION TO POWER: THE HISTORY OF FDA REGULATION OF THE DRUG INDUSTRY.....	124
A. LABELING FRAUD: THE FIRST BENCHMARK OF FDA REGULATION.....	125
B. DRUG SAFETY: THE SECOND BENCHMARK OF FDA REGULATION.....	127
C. SAFETY AND EFFECTIVENESS: THE THIRD BENCHMARK OF FDA REGULATION.....	129
D. FDA REGULATION OF NEW DRUG APPROVAL UNDER THE DRUG EFFICACY AMENDMENTS.....	133
E. FDA REGULATION OF GENERIC DRUG APPROVAL UNDER THE DRUG EFFICACY AMENDMENTS.....	137

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F. <i>GENERIC/INNOVATOR FORCED COMPROMISES—THE HATCH-WAXMAN AMENDMENTS</i>	143
II. OVERSTEPPING THE BOUNDS: THE FDA’S OVERBROAD REGULATION OF DRUG ACCESS AND AVAILABILITY	146
A. <i>THE RISE OF PHARMACEUTICAL ADVERTISING</i>	147
B. <i>FDA REGULATION OF PHARMACEUTICAL ADVERTISING</i>	151
C. <i>FDA REGULATION OF OFF-LABEL DRUG PROMOTION</i>	152
D. <i>BALANCING PHYSICIAN AUTONOMY, PHARMACEUTICAL INNOVATION AND PUBLIC HEALTH</i>	154
E. <i>JUDICIAL INVALIDATION OF FDA RESTRICTIONS ON COMMERCIAL SPEECH</i>	157
III. POLICY CONSIDERATIONS: CAN THE FDA CATCH UP TO THE FUTURE?	162
A. <i>THE DOUBLE-EDGED SWORD OF DRUG REGULATION</i>	163
B. <i>MEDICAL LIABILITY RESULTING FROM OFF-LABEL USE</i>	167
C. <i>MANUFACTURER LIABILITY RESULTING FROM OFF-LABEL USE</i>	172
D. <i>PROPOSALS FOR FDA REFORM</i>	180
CONCLUSION: THE BIG PICTURE.....	185

INTRODUCTION: SETTING THE STAGE

Since the first caveman’s first headache, people have always sought a cure for what ails them: a pill, a potion, a magic elixir that heals disease and restores health and happiness. While no medical panacea exists, the progress that modern science has made, and continues to make, in creating therapeutic medicines is nothing short of astonishing. The rapid pace of pharmaceutical innovation over the last century has certainly redounded to the patient’s benefit and, *a fortiori*, to the pharmaceutical industry’s profit. At the same time, government institutions and policies have been struggling to keep pace and address the social implications of

industry advances through the regulation of and support for public health needs.

As society grapples with the evolving and increasingly sophisticated nature of the pharmaceutical industry, the “big picture” in healthcare remains, of course, to take care of the patient. Any and all medical decision making, therefore, should follow the primary exhortation of the Hippocratic Oath: The first thing is to do no harm.¹ Although physicians are no longer required to take the oath upon entering practice, its tenet must remain at the forefront of modern medical care. Medical prescribing decisions can be complicated, particularly when better health outcomes are associated with increased costs. This truth is evidenced by the cast of legislators, policymakers, insurers, healthcare providers, and consumers who regularly weigh in on the complex healthcare issues largely unforeseen by previous generations. This Note will focus on the influence of the three principal players on the pharmaceutical healthcare stage, each with distinct and complementary roles: the physician as healer, the public sector regulator as protector, and the private sector investor as innovator.

Physicians, as licensed health care practitioners, are professionally obliged to serve and protect the best interests of their patients. Medical ethics dictate that a physician weigh the benefit of any intervention against its potential harm in determining a patient’s course of treatment. Indeed, physicians have wide discretion under law to make these types of individual patient assessments. They can provide medical services and prescribe approved drugs almost entirely as they see fit. This professional autonomy is considered the cornerstone of medical practice.²

¹ *Greek Medicine: The Hippocratic Oath*. (Michael North trans., 2002), http://www.nlm.nih.gov/hmd/greek/greek_oath.html. See also Hippocrates, *Oath*, in 1 HIPPOCRATES 299 (W.H. Jones trans. 1962).

² For a review of how physicians established sovereignty over the domain of medical practice through licensing laws, medical education requirements and private insurance programs, see Mark A. Hall, *Institutional Control of Physician Behavior: Legal Barriers to Healthcare Cost Containment*, 137 U. PA. L. REV. 431, 445–49, 453 (1988) (broadly delimiting the activity that constitutes medical practice as “*diagnosing, treating, or prescribing* for any physical or mental condition”) (emphasis added).

Although doctors are under few direct regulatory controls regarding the dispensation of their services and their prescribing habits, other aspects of the United States healthcare system are highly regulated by the public sector. The United States Food and Drug Administration (FDA) is an agency of the United States Department of Health and Human Services, authorized by Congress to promote the safety and efficiency of prescription drugs and medical devices placed on the U.S. market.³ The FDA's official mission is threefold: to protect public health by ensuring that safe and effective products reach the market in a timely manner; to monitor products for continued safety after they are in use; and to help the public get the accurate, science-based information needed to improve and maintain health.⁴ The FDA strives to accomplish this mission through the use of product standards and regulations, to delineate the requirements that the pharmaceutical industry must follow, to control drug product safety, and to provide accurate information to health professionals and consumers.⁵

Modern medical practice relies extensively on the use of prescription drugs, which are marketed to physicians and marketed, but not distributed, directly to consumers by private drug manufacturers.⁶ The FDA retains a large degree of regulatory oversight of clinical practice, therefore, through its regulation of drug products supplied by the private pharmaceutical industry. The FDA has extensive authority over the advertising and

³ The FDA's authority is derived from a complex statutory and regulatory scheme, a majority of which is embodied in the Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301–399 (2004). See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998).

⁴ 21 U.S.C. § 393(b) (Supp. III 1994) (amended 1997) (codifying the FDA's mission). See also *An FDA Overview: Protecting Consumers, Protecting Public Health* (2004), <http://www.fda.gov/oc/opacom/fda101/fda101text.html> (describing the FDA's public health mission).

⁵ *Id.*

⁶ A drug manufacturer is a business entity, usually a pharmaceutical company, that produces and prepares drugs for distribution from the original place of manufacture to the person or entity who makes final delivery or sale to the consumer. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 381 (2002) (reviewing the definition of drug manufacturing in various state statutes). For the purposes of this Note, a drug manufacturer will generally refer to the private entity responsible for manufacturing, distributing and promoting the drug(s) in question.

marketing claims that drug manufacturers may make for all approved pharmaceuticals, whether to patients or physicians. FDA regulations mandate that all drug labeling claims, advertisements and other industry-sponsored promotional statements provide physicians with the necessary information to optimally prescribe the drug products as approved and provide patients with adequate directions for those uses. Taken together, the FDA's regulatory reach over the private sector is panoptic—the FDA controls nearly every aspect of communication that the drug industry has with every prescriber and consumer of pharmaceutical products in the United States.

An underlying premise of FDA regulation is that the public needs protection from the products of the profit-seeking private sector. The FDA's platform is limited, however, in that the agency has neither the authority nor the capability to evaluate the treatment needs of individual patients. As such, the FDA does not seek to regulate the practice of medicine or to interfere with the practitioner-patient relationship.⁷ The FDA accepts that it is well within a physician's discretion to prescribe any approved drug product for uses or in treatment regimens or patient populations not included in the approved labeling.⁸ Physicians are familiar with the drug approval process and are deemed able to critically evaluate the utility of a drug for specific treatment purposes.⁹ As a matter of policy, therefore, it is left to the physician's unfettered discretion to prescribe an approved drug for an indication or in a manner other than that for which it was approved, i.e., for "off-

⁷ See Federal Food, Drug and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 396 (1997)) ("Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.").

⁸ Once the FDA has approved a new pharmaceutical product for prescription sale and use for one purpose, that product is available for physicians to prescribe it to patients for other purposes. *Id.* The only exception to this rule is controlled substances (i.e., narcotics), which can only be legally prescribed for approved uses. See generally Comprehensive Drug Abuse Prevention and Control Act, Pub. L. 91-513, 84 Stat. 1242 (1970) (codified as amended at 21 U.S.C. §§ 801-971).

⁹ Indeed, the FDA has often acknowledged that valid new uses for approved drugs are often first discovered through serendipitous clinical observations. 59 Fed. Reg. 59,820 (Nov. 18, 1994) (citing FDA Drug Bulletin 12:4-5, 1982).

label” use.¹⁰ By contrast, any direct promotion by a drug manufacturer of off-label drug use is strictly barred. The FDA’s position is that any private industry promotion, e.g., labeling or marketing, of unapproved drug uses may result in both physicians and patients being unable to make informed and unbiased decisions.¹¹

Off-label drug use is pervasive in the United States and both its risks and benefits are widely recognized by many government policies and practices. Many of these practices form the centerpiece of federal health policy and, as such, can serve to both exemplify and contextualize the ineradicable tension that exists between public sector regulation of and private sector investment in U.S. healthcare.

Longstanding controversies in the healthcare arena generally turn on: (1) the acceptable level of regulatory oversight that balances both the complex economic and policy demands of the medical and pharmaceutical industries; and (2) the demands of doctors to be protected from all forms of encroachment on their medical judgments. Recent legislative measures have focused on improving drug safety by tightening FDA supervision and/or government enforcement of the production and dissemination of information concerning off-label drug use by the private sector.¹² This Note will address such lawmaking as part of the larger issue of balanced oversight in the pharmaceutical industry. It will analyze the legal scope and ramifications of progressive governmental regulation of the increasingly fecund and lucrative business of the private pharmaceutical industry in three parts.

Part I will review the historical development of the FDA’s administrative authority and its increasingly expansive regulation of pharmaceutical drug approval, labeling and marketing in the United States. It will review the evolution of the FDA, from its aborning role as a watchdog agency for labeling fraud to its full

¹⁰ “Off-label” use includes treating a condition not indicated on the FDA-approved label, or treating the indicated condition but varying the dosing regimen, patient population, or providing a drug combination other than as indicated in the label. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998).

¹¹ See *supra* note 9, at 59,821–22.

¹² See discussion *infra* Part III.

grown position as the major regulator of drug marketing and promotion. This part will examine the various social events that have led to broadening amendments in FDA law over the past century, including the rise of the generic drug industry and the FDA's powerful influence over the commercial and marketing warfare between branded pharmaceutical and generic drug manufacturers.¹³

Part II will examine the overreach of the FDA's regulatory scheme for controlling drug access and availability through the regulation of information dissemination. It will describe the changes in law that led to an upsurge in the promotional practices of pharmaceutical manufacturers and the FDA's reactive attempts to control those practices. It will review the various court rulings that forced the FDA to yield to the First Amendment's directive to let drug manufacturers disseminate information to, and communicate with, prescribing physicians. This part will also consider the proper influence of off-label drug promotion and use on competitiveness in the drug marketplace and on the practitioner-patient relationship.

Part III will examine the costs to all parties of the FDA's regulation of drug manufacturers' promotional practices and of, at least indirectly, physicians' prescribing practices. It will assess both the medical and manufacturer liability associated with FDA noncompliance, including the increasingly aggressive civil and criminal enforcement measures being taken against both drug companies and individuals. This part will examine current legislative proposals for FDA reform and the policy considerations underlying such reform, including the important need to improve post-marketing testing and surveillance, to increase drug safety research on the expanded uses of approved drugs and to incentivize manufacturers to obtain regulatory approval of off-label uses.

¹³ A branded pharmaceutical manufacturer is one that invests in the research, development, approval, and marketing of "innovator" or brand-name drugs. By contrast, a generic drug manufacturer is one that typically does not engage in novel research but instead copies the active ingredient in an already approved new drug to bring a competing non-brand-name product to market. A generic drug contains the same active ingredient, but not necessarily the same inactive ingredients, as the innovator drug.

This Note will conclude by reflecting upon the need to strike a politic balance between consumer protection, physician autonomy and pharmaceutical industry freedom to communicate and innovate. Such policies are certain to carry a heavy burden of public interest because of their direct impact on the development, availability and cost of prescription pharmaceuticals in the United States.

I. THE FDA'S ASCENSION TO POWER: THE HISTORY OF FDA REGULATION OF THE DRUG INDUSTRY

The FDA has broad jurisdiction over three major categories of products—foods, drugs and devices, and cosmetics.¹⁴ The precise boundaries of each of these areas are constantly being challenged and refined by both the legislature and the courts.¹⁵ In order to understand the current scope of the FDA's jurisdiction over pharmaceutical access and availability, this Note begins by examining how the FDA's authority over this area has evolved historically.

¹⁴ As defined in the Federal Food, Drug and Cosmetics Act, the term "food" comprises articles or components thereof used for food or drink for man or other animals, and chewing gum. 21 U.S.C. § 321(f) (2004). The term "drug" comprises "products intended for use in the diagnosis, cure, mitigation, treatment, prevention of disease or otherwise intended to affect the structure or any function of the body of man or other animals." *Id.* § 321(g)(1). The term "device" comprises "any instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article" intended for the same uses as drugs, above. *Id.* § 321(h). The term "cosmetic" comprises "articles or components thereof intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance," but excluding soap. *Id.* § 321(i).

¹⁵ For example, the legislature is currently addressing the issue of whether biologic drugs, i.e., therapeutic protein products, should fall under the FDA's jurisdiction or whether such complex proteins are sufficiently different from traditional drug products to warrant exemption from FDA authority. *See* discussion *infra* notes 242–245. In the past, the courts have also weighed in on the bounds of such authority, e.g., by specifically excluding nicotine and tobacco products from the FDA's jurisdiction over drug products. *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 126 (2000).

A. Labeling Fraud: The First Benchmark of FDA Regulation

In the late 1800's, there were few restrictions on drugs. Drugs were branded as cure-alls, snake oils and elixirs that claimed to relieve all ailments.¹⁶ In 1906, the Department of Agriculture's Bureau of Chemistry, as forerunner of the FDA, was empowered to regulate drugs under the Pure Food and Drugs Act ("the 1906 Act").¹⁷ That act prohibited interstate commerce in "adulterated" or "misbranded" drugs. A drug was generally considered to be adulterated if its strength, quality or purity differed from the professional standard.¹⁸ A misbranded drug was one that was sold under another name or sold without a label that properly listed the quantity and proportion of the drug.¹⁹ This latter definition was later amended to also prohibit false or misleading claims regarding the therapeutic effect of the drug.²⁰ There was no distinction made between prescription and proprietary, or over-the-counter, drug products under the 1906 Act.²¹ It provided for a general seizure and disposal of products that violated its labeling requirements.²²

¹⁶ In fact, the avowed broad therapeutic effect of many drugs on the market was likely attributable to the high alcohol content of the various medications at the time.

¹⁷ Pure Food and Drugs Act, ch. 3915, §§ 1-13, 34 Stat. 768, (1906) (repealed 1938), available at <http://coursesa.matrix.msu.edu/~hst203/documents/pure.html>. The Bureau of Chemistry changed its name to the Food, Drug and Insecticide Administration in 1927. This was then shortened to the Food and Drug Administration in 1931. In 1940, jurisdiction over the agency was transferred to the Federal Security Agency, which later became the Department of Health and Human Services. See Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 891 n.12 (1996) (citations omitted).

¹⁸ The U.S. Pharmacopoeia and National Formulary published the official standards for the strength, quality, and purity of drugs and for the tests to make such determinations. These "USP" standards are still recognized today. See David L. Stepp, *The History of FDA Regulation of Biotechnology in the Twentieth-Century*, 46 FOOD & DRUG L.J. 1, 6, (1999) (citing 21 U.S.C. §§ 351(a)-(b)).

¹⁹ *Id.* at 6-7 (citing 21 U.S.C. § 351(j)).

²⁰ The Sherley Amendment of 1912, ch. 352, 37 Stat. 416 (1912). This amendment was passed in response to the Supreme Court's ruling that the 1906 Act applied only to false statements made about the identity of the drug (e.g., strength, quality, purity) and not to statements as to curative effect (e.g., effective as a cure for cancer). See *United States v. Johnson*, 221 U.S. 488 (1911).

²¹ Mary T. Griffin, *AIDS Drugs and the Pharmaceutical Industry: A Need for Reform*, 17 AM. J. L. & MED. 363, 375 n.69 (1991) (citation omitted).

²² The 1906 Act, *supra* note 17, at § 10.

The Bureau of Chemistry did little to enforce this drug regulatory regime in the midst of the pro-business political climate of the 1920s.²³ Moreover, the government had the difficult burden of proving misrepresentation. It had to monitor the manufacturer to demonstrate actual fraud, which amounted to an after the fact look at a product on the market.²⁴ The 1906 Act served its somewhat “laissez-faire” purpose of at least putting the public on notice about the contents of commercially available drug products. It did not, however, address either the safety or efficacy of the drug products, other than in the context of false or misleading claims of therapeutic effect. Despite its obvious shortcomings, the FDA touts the 1906 Act as a “pillar of the Progressive era.”²⁵

The next major change in U.S. drug regulation occurred after a healthcare crisis in 1937. In that year, many children died after ingesting a liquid formulation of a publicly distributed drug that had been tested for flavor, but not safety, before marketing.²⁶ The public outcry galvanized Congress to action—a disaster-based call repeated in the context of drug regulation a number of times over the following years. Congress recognized that the FDA’s authoritative reach needed to extend beyond labeling standards. It needed to provide a substantive pre-marketing review of drugs. Shortly thereafter, President Franklin Roosevelt signed the first

²³ See Griffin, *supra* note 21, at 376.

²⁴ Myron L. Marlin, *Treatment INDs: A Faster Route to Drug Approval?* 39 AM. U. L. REV. 171, 175 (1989).

²⁵ John P. Swann, *The History of the FDA*, in THE HISTORICAL GUIDE TO AMERICAN GOVERNMENT (George Kurian ed., Oxford University Press 1998), *excerpt available at* <http://www.fda.gov/oc/history/historyoffda/fulltext.html>. *But see* Marlin, *supra* note 24, at 174 n.28 (describing the concerns of drug manufacturers that the 1906 Act would severely curtail business).

²⁶ The drug was an antibiotic known as sulfanilamide. The elixir contained sulfanilamide powder dissolved in diethylene glycol to make it a palatable liquid for children. Drug manufacturers did not know at the time that the liquid composition was highly toxic and the 1906 Act was ineffective in preventing this disaster because it only operated after the fact to police the adulteration or misbranding of items already on the market. See Stepp, *supra* note 18, at 8–9. See also Joseph G. Contrera, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonious will International Pharmaceutical Regulations Become?*, 8 ADMIN. L.J. AM. U. 927, 934 n.26 (1995) (noting that today ethylene glycol is most commonly used as automobile anti-freeze).

nationwide consumer protection law—the Federal Food, Drug and Cosmetic Act of 1938 (FDCA).²⁷

B. Drug Safety: The Second Benchmark of FDA Regulation

The FDCA required, for the first time, that drug manufacturers test all new drugs for safety and provide the results of the testing to the FDA in a New Drug Application (NDA), prior to bringing the new drug to market. An NDA would include a description of the drug's composition, the results of the safety testing, and the manufacturing and quality control processes for the commercial product. No new drugs could be marketed until proven safe for use under the conditions described on the label and approved by the FDA. In an effort to mollify the overwhelming concerns of drug manufacturers, the FDCA grandfathered all drugs that were already on the market from the new testing requirements, provided that the drug's labeling retained the same representations concerning the conditions of its use as it did when it was approved under the 1906 Act.²⁸

The FDA reviewed each NDA for drug safety, but not efficacy. If the NDA satisfied the regulatory criterion of safety and the FDA took no action to reject the NDA within a fixed period of time after its filing (typically sixty days), it became effective and the drug was de facto approved for marketing.²⁹ Under the FDCA, the FDA tightly controlled all aspects of drug marketing, mandating that the drug product be labeled with extensive safety warnings and directions for use. Drug manufacturers initially retained discretion over the classification of drugs as prescription or non-prescription. However, after several episodes of consumer misuse, an amendment to the FDCA distinguished between drugs that could be marketed with adequate directions for use by laymen and those that were not considered safe for lay use even with directions.³⁰

²⁷ Federal Food, Drug and Cosmetic Act, ch. 675, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301–399 (2006)).

²⁸ See Walsh & Pyrich, *supra* note 17, at 894.

²⁹ See 21 U.S.C. § 355(c) (1938) (amended 1994); Hoffmann-LaRoche, Inc. v. Weinberger, 425 F. Supp. 890, 892 (D.D.C. 1975).

³⁰ Durham-Humphrey Amendment, ch. 578, 65 Stat. 648 (1951) (codified as amended at 21 U.S.C. § 353 (2004)).

The former class of drugs was categorized as non-prescription drugs that could be dispensed over-the-counter (“OTC”). The latter were categorized as prescription drugs that could only be dispensed by a licensed medical practitioner (i.e., “Rx only”).³¹

The FDCA created a new healthcare landscape and, effectively, architected the FDA’s role as guardian of public safety in the drug industry. The FDCA also encouraged physician dependence, by establishing new privileges for licensed physicians to become the arbiters of the FDA’s growing system of regulations for prescription drugs. As a result, the medical profession enjoyed an institutionalized and legitimized increase in status throughout the 1950’s, when patients relied heavily on their physicians to determine the proper treatments.

Not surprisingly, the pharmaceutical industry vehemently opposed these FDCA mandated changes, arguing that the required evidence of safety would cripple research efforts and delay getting new drugs to market, not to mention undermine the consumers’ freedom to self-medicate.³² The standing of drug makers relative to government regulators would continue to shift and reform over the years, as the result of the FDA’s ongoing attempt to create a balanced level of public oversight of the healthcare industry.

The next major shift in FDA regulatory policy occurred in response to another healthcare crisis, this time associated with the sedative drug thalidomide. Thalidomide was a non-barbiturate (and therefore non-addictive) sleep-aid that was widely used in Europe in the late 1950’s. Thalidomide was also widely prescribed off-label to pregnant women across Europe to relieve morning sickness.³³ By 1962, it had become clear that the drug was teratogenic—it damaged the fetus and caused birth defects.³⁴ Thalidomide was pending approval in the United States when this

³¹ *Id.*

³² See Griffin, *supra* note 21, at 376. The pharmaceutical industry’s cries of “the sky is falling” became a leitmotif every time the FDA regulations were changed in future years. The refrain is still being played today.

³³ See Contrera, *supra* note 26, at 935 n.33.

³⁴ *Id.* Thousands of babies were born with truncated limbs that resembled flippers. The disease was known as *phocomelia* (Greek for “seal limb”). See also Stepp, *supra* note 18, at 13.

devastating aftereffect was discovered.³⁵ The fear of such an event taking place in the U.S. spurred Congress to enact more stringent drug regulation laws.

C. Safety and Effectiveness: The Third Benchmark of FDA Regulation

The 1962 Kefauver-Harris Amendments, also coined the Drug Efficacy Amendments, essentially put in place the protectionist system of drug regulation that we have today.³⁶ They forbade the shipment in interstate commerce of any new drug that the FDA had not formally approved as to both the drug's overall safety and efficacy. In order for a drug to meet these requirements, the drug's sponsor needed to conduct three phases of clinical trials. Phase I determined the toxicity of the drug in humans; Phase II tested the therapeutic effect in patients with the target illness; and Phase III consisted of an expanded series of typically blinded comparative clinical trials with a wider range of patients.³⁷ Moreover, before the human clinical trials could even commence, the drug's sponsor was required to file an Investigational New Drug Application (INDA), to approve the "investigational" use of the drug. The INDA served as a request for FDA authorization to administer the unapproved drug to humans.

The INDA itself required substantial data about the drug, including its pharmacological activity and acute toxicity potential in animals (so-called pre-clinical trials), along with information detailing the use of good laboratory practices by the sponsor and information on any previous human experience with the drug (e.g.,

³⁵ FDA approval had been delayed pursuant to investigations on potential adverse neurological reactions. In 1962, President Kennedy bestowed the Distinguished Federal Civil Service Award on FDA physician Frances Kelsey, who delayed approval, even though the delay may have been more bureaucratic than investigative. Steven B. Harris, *The Right Lesson to Learn from Thalidomide* (1992), available at <http://w3.aces.uiuc.edu:8001/Liberty/Tales/Thalidomide.html>.

³⁶ Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. §§ 321, 331-32, 348, 351-53, 355, 357-60, 372, 374, 376, 381 (1970)). For an enlightening discussion of the political landscape leading up to this legislation, see Griffin, *supra* note 21, at 375-79.

³⁷ The phases were often permitted to overlap. Long term toxicity tests in two species of animals were also performed alongside the clinical trials. See Contrera, *supra* note 26, at 935 n.35.

marketing in another country). The INDA was also required to detail the course of the proposed human clinical trials. The FDA and a local Institutional Review Board (IRB) needed to approve the INDA before any shipment or administration of the drug for diagnostic and therapeutic testing in humans, i.e., the clinical trials, was permitted by law.³⁸

The subsequent NDA, for approval to market the drug, was essentially a compendium of the INDA and the human clinical data. The NDA contained detailed and extensive reports on the animal studies and human trials; a description of the drug's components, chemical formulation and manufacturing conditions; and samples of the drug and of the proposed packaging.³⁹ The FDA considered all of this information in assessing the drug's effectiveness and safety for human consumption and in providing appropriate clearance for labeling.⁴⁰

The regulatory scheme of the Drug Efficacy Amendments gave the FDA comprehensive control over all aspects of the design and implementation of the pre-clinical research and subsequent clinical trials route to the marketplace.⁴¹ This process placed the ultimate responsibility on the drug sponsor (usually the manufacturer) to

³⁸ See generally 21 U.S.C. § 355 (1970) (amended 2004) and 21 C.F.R. § 312.22(a) (2007) (outlining general requirements for INDA submission). See also Stepp, *supra* note 18, at 13–14.

³⁹ 21 U.S.C. § 355 (1970).

⁴⁰ Consistent with the 1938 version of the statute, a *de facto* clause held that approval (i.e., clearance for labeling) became effective if the FDA did not approve the application or give the applicant notice of an opportunity for hearing within a fixed period of 180 days. 21 U.S.C. § 355(c) (1970) (amended 1994). In post-1962 practice, however, this clause had no real effect. The FDA always took some action on the application within the fixed period that required some further action (e.g., additional testing) by the drug sponsor. These requests served to delay the FDA's consideration and eventual issuance of an order either approving the application or else refusing to approve the application. 21 U.S.C. § 355(d) (1970) (amended 1994). NDA applicants were frustrated with the FDA's informal practice of restarting the clock each time additional information was submitted in response to these, often multiple, FDA requests. The applicants, however, were hesitant to press for a ruling that could be adverse. Thus, despite the standing statutory requirement for the FDA to "consider" an NDA within six months, the actual approval time was typically upwards of three years.

⁴¹ Walsh & Pyrich, *supra* note 17, at 901 (aptly noting that "[t]he FDA has maintained tight control of this marketplace ever since [the FDCA was enacted] and . . . the 1962 Amendments have aided the FDA in this regard").

provide sufficient evidence that the proposed drug was a safe and effective therapeutic and had a risk-benefit profile appropriate for use to treat human disease.⁴² In the past, it was the physicians and end-user consumers who had generally judged a drug's efficacy, on a person by person basis. Under the new regime, all drug safety and efficacy determinations were now comprehensively under the aegis of the FDA.

Not surprisingly, the drug industry remonstrated the Drug Efficacy Amendments *ab ovo*. Business interests trumpeted familiar complaints about how the "drug lag" associated with the new approval process would reduce pharmaceutical productivity and competitiveness.⁴³ Indeed, the expense and duration of the human clinical trials shifted the burden to drug manufacturers to determine drug efficacy prior to approval. The Drug Efficacy Amendments also imparted more of the decision-making power to the FDA, and took away some freedom of choice from the doctors and patients.⁴⁴ The FDA maintained that the broad brush legislation, while sweeping in nature, was laudable in that it would ensure that sufficient knowledge production about the effectiveness of a drug preceded its diffusion into practice.

Regulatory critics concluded that the time and money spent by drug manufacturers seeking FDA approval raised costs and caused significant delays in drug development and in the introduction of

⁴² The drug sponsors' additional responsibilities included: selecting investigators to perform studies on the drug; monitoring the progress of the drug tests; ensuring that the investigators comply with the regulations; evaluating the evidence of the safety and efficacy of the drug; detailing the results of the concluded studies in submissions to the FDA; and discontinuing any investigation and use of the drug upon the discovery of unreasonable and significant risk to the public (both pre- and post-marketing). See Marlin, *supra* note 24, at 179–80.

⁴³ See e.g., *supra* notes 25 and 32 and accompanying text.

⁴⁴ Interestingly, the legislative intent of the Drug Efficacy Amendments was purportedly, in part, to ensure that physicians would get ready access to reliable information about drug products via the clinical trials data. During the congressional hearings, numerous academic scientists testified in support of imposing a proof of effectiveness requirement, criticizing the unreliability of impressionistic judgments about drug efficacy made by individual physicians. See Lars Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 436, nn.270–72 (2002).

new drugs on the post-1962 market.⁴⁵ Regulatory proponents generally dismissed these criticisms as self-serving rhetoric and argued that the social benefits of the Drug Efficacy Amendments outweighed their potential costs. With the institutional memory of the thalidomide tragedy still at the forefront of the debate, many believed that the drug industry was operating under a business paradigm that, if left unchecked, would certainly incur more drug-related injuries. The FDA, thus, took a watchful, and perhaps somewhat imperious, stance in vigorously enforcing the prophylactic purpose of the Amendments.

On balance, the Drug Efficacy Amendments sought to mitigate two opposing consumer health and safety risks inherent in the drug approval process—the potential for inappropriate approval of dangerous or therapeutically ineffective drugs and the potential for undue delay in bringing safe and effective drugs to market. Indeed, the Supreme Court has construed the nature and ambit of the Amendments as *requiring* the FDA to prevent the marketing of any drug where the potential for inflicting death or physical injury is not sufficiently offset by the possibility of therapeutic benefit.⁴⁶ The Supreme Court reasoned that the safety of any drug inherently depends on its therapeutic effectiveness for that indication and a drug can be determined safe and effective based on the

⁴⁵ See, e.g., Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 JOURNAL OF POLITICAL ECONOMY 1049, 1049–91 (1973) (concluding that the penalties imposed by the marketplace on sellers of ineffective drugs prior to 1962 provided a sufficient deterrent to drug manufacturers and the FDA's increased post-1962 power was overly burdensome).

⁴⁶ *United States v. Rutherford*, 442 U.S. 544, 556 (1979). In this class action suit, terminally ill cancer patients sought to enjoin the Government from interfering with the interstate shipment and sale of a drug (Laetrile®) that was not FDA approved. The Supreme Court reversed the Tenth Circuit's ruling that the safety and effectiveness requirements of the FDCA had no reasonable application to terminally ill cancer patients and instead held that the statute inherently encompassed treatments for terminal diseases and did not foreclose all resort by patients to experimental cancer drugs for whom conventional therapy was unavailing. ("Nothing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendments, which added the current safety and effectiveness standards in § 201(p)(1), suggests that Congress intended protection only for persons suffering from curable diseases.") *Id.* at 552–53.

circumstances of its use, e.g., to prolong life or reduce pain, in the class of patient being treated.⁴⁷

In other words, the FDA was not permitted to sidestep its own regulations for terminally ill patients and peremptorily opt for speed over safety. Rather, the FDA was required to assess the safety and efficacy of any drug for the single and specific use for which it was seeking approval. Thus, a drug for the treatment of late-stage cancer, with long-term safety concerns or certain known side effects, might be approved for use in terminally ill patients because of the time-sensitive context of any efficiency measurement for that use. By contrast, if the drug sponsor sought approval for the same drug for treatment of a less severe or less urgent problem, the FDA might find that the imputed benefits would not outweigh the potential harm to the patient, given the nonessential nature of the treatment in that population or for that use.⁴⁸

D. FDA Regulation of New Drug Approval Under the Drug Efficacy Amendments

In a concerted effort to craft an appropriate and timely drug approval process, the FDA set forth specific guidelines to evaluate the safety and efficacy of proposed drugs. Under these guidelines, the FDA decided that *safety* could legitimately be evaluated on an overall product basis, such that an approved product would be deemed safe for all uses. By contrast, the FDA decided that the *efficacy* requirement, newly introduced in the Drug Efficacy Amendments, needed to be evaluated on the basis of a particular therapeutic purpose, such that each new therapeutic use of a drug required individual approval.⁴⁹

⁴⁷ *Id.* at 556–57 (describing the “special sense in which the relationship between drug effectiveness and safety has meaning in the context of incurable illnesses”).

⁴⁸ Much later, in a mobilized response to the AIDS epidemic in the late 1980’s, Congress passed legislation that provided the FDA with additional resources to accelerate the approval process for drugs to treat life-threatening diseases. Under the new law, the FDA guaranteed that drug reviews would be completed within as little as six months for life-saving drugs in priority review categories. See Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992). This law has been thrice renewed and is still in place. See *infra* note 252.

⁴⁹ See Stepp, *supra* note 18, at 14.

Because proof of effectiveness was not generalizable to a given drug product, the FDA introduced a process whereby the drug sponsor had to file a Supplemental New Drug Application (SNDA) for separate FDA approval of each new therapeutic use of an approved drug product, i.e., one the FDA had determined was safe for all purposes but only effective for that approved use.⁵⁰ As a consequence, in order for a drug manufacturer to change the label of an already-approved drug, or to market a new aspect of the drug, the manufacturer was required to file an SNDA and obtain approval for the change. New aspects of a drug that required a label change and thus an SNDA included, *inter alia*, a new indication, dosage, strength, formulation or manufacturing process.⁵¹

Drug manufacturers loudly inveighed against the SNDA process because SNDAs often took longer to approve than the original NDAs. Drug manufacturers also incurred significant costs complying with the SNDA regulations, which reduced the monies that could be spent on research and development for new drugs or for new uses of approved drugs.⁵² Viewed through those lenses, the supplementary regulations also served to delay the availability of new treatments for patients while drug manufacturers spent time

⁵⁰ 21 C.F.R. § 314.70 (1994). See Nina J. Crimm, *A Tax Proposal to Promote Pharmacological Research, to Encourage Conventional Prescription Drug Innovation and Improvement, and to Reduce Product Liability Claims*, 29 WAKE FOREST L. REV. 1007, 1029–30 (1994).

⁵¹ SNDAs had to be filed with specific Effectiveness Supplement Code Indications, to identify the requested label change to be reviewed. Example Indications are as follows:
SE1 = A new indication or a significant modification of an existing indication, including removal of a major limitation to use, such as second line status (i.e., for patients who have already tried one treatment).

SE2 = A new dosage regimen, including an increase or decrease in daily dosage or a change in frequency of administration.

SE3 = A new route of administration.

SE4 = A comparative efficacy claim naming another drug, including a comparative pharmacokinetic claim.

SE5 = A change in sections other than the indications and usage section that would significantly alter the patient population to be treated, such as addition of pediatric use and/or dosing information or geriatric use and/or dosing information.

See FDA Drug Approvals List, Notes on Effectiveness Supplement Code Definitions, available at <http://www.fda.gov/cder/da/da.htm>.

⁵² See Walsh & Pyrich, *supra* note 17, at 887–89 (enumerating the costs of regulatory compliance).

and money trying to expand the scope of FDA-approved drug uses.⁵³

Complaints aside, the drug manufacturers had no choice but to follow the SNDA process if they wanted to legally market a new use for an existing drug product. Failure to file an SNDA and to obtain FDA approval for the label change before a new use for a drug was introduced into the market could result in the withdrawal of the FDA's approval of the original NDA.⁵⁴ Practically speaking, the SNDA process served to further enhance the FDA's regulatory control over drug labeling and the dissemination of information concerning appropriate drug use under that label to consumers and physicians.

The Drug Efficacy Amendments also provided for a retrospective FDA review to assess the effectiveness of each of the labeled uses claimed for drug products already on the market.⁵⁵ Thus, in addition to reviewing the efficacy of new drugs, the FDA also began to investigate the effectiveness of old drugs.⁵⁶ The practical intent of this look-back was to apply the efficacy requirements introduced by the Amendments to drugs whose market entry had required only a demonstration of safety under the original FDCA of 1938.⁵⁷ Unlike the situation with the 1906 Act and the FDCA, there was no large scale grandfathering.⁵⁸

Pharmaceutical companies were given a two year grace period following the enactment of the Amendments to submit scientific

⁵³ The FDA has since created certain processes for obtaining expedited SNDA review, if a delay in drug marketing due to the pre-approval requirement would result in an "extraordinary hardship." Crimm, *supra* note 50, at 1099 n.105. Expedited review, however, is used only in emergency situations, such as a potential out-of-stock situation. *Id.* See also 21 C.F.R. § 314.70(b) (1994).

⁵⁴ 21 U.S.C. § 355(e) (1970) (amended 2004).

⁵⁵ See *Am. Pub. Health Ass'n v. Veneman*, 349 F. Supp. 1311, 1313–14 (D.D.C. 1972).

⁵⁶ See *id.*

⁵⁷ See *id.* at 1314.

⁵⁸ See *id.* The Drug Efficacy Amendments did grandfather certain drugs already in use, but this exemption from the new approval requirements was highly limited and required, *inter alia*, the drug to be already "generally recognized . . . [among qualified experts] . . . as safe and effective under the conditions already prescribed, recommended or suggested in the labeling." 21 U.S.C. § 321(p)(1) (2006); see also Walsh & Pyrich, *supra* note 17, at 898–99.

data in support of their efficacy claims.⁵⁹ Initially, the drug industry failed to comply, but after several extensions and penalties, the vast outpouring of submissions overwhelmed the FDA.⁶⁰ To overcome the inevitable back log, the FDA outsourced review of the data to expert panels established by the National Academy of Science and National Research Council (NAS-NRC).⁶¹

The expert panels reviewed each approved drug by class.⁶² NDA holders were invited to furnish the panels with the best available scientific data to establish efficacy of their drugs.⁶³ On the basis of that information, the panels applied a “substantial evidence” test to determine whether the drug was effective for its intended and labeled uses.⁶⁴ If substantial evidence of effectiveness was lacking, marketing clearance for the drug was withdrawn.⁶⁵ Because the manufacturer carried the burden of providing the required substantial evidence of efficacy, the test was intended to strengthen the protection afforded the public by prohibiting the continued marketing of drugs whose effectiveness had not been adequately established.⁶⁶ A less sanguine view of the review was that the required testing plucked the efficacy judgment from the hands of physicians and consumers and placed it within the stronghold of FDA regulation.⁶⁷

The stringent and highly controversial FDA review took years to complete. Further, only a minority of the previously approved drugs passed the “substantial evidence” test of efficacy upon first

⁵⁹ *Veneman*, 349 F. Supp. at 1314.

⁶⁰ *Id.*

⁶¹ *See id.*

⁶² *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 614 (1973).

⁶³ *Id.* at 614–15

⁶⁴ 21 U.S.C. § 355(d) (2003) defines “substantial evidence” as: “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 prescribed, recommended, or suggested in the labeling.” *Id.* at 613 n.3.

⁶⁵ *See id.* at 617.

⁶⁶ *See id.*

⁶⁷ *See id.* at 619.

round review.⁶⁸ Rather, most of the previously approved drugs received intermediary classifications of “probably effective” and “possibly effective,” which required drug manufacturers to furnish further data to establish efficacy to continue marketing.⁶⁹ The previously approved drugs that ultimately received favorable efficacy determinations were permitted to remain on the market under renewed NDAs.⁷⁰

E. FDA Regulation of Generic Drug Approval Under the Drug Efficacy Amendments

The Drug Efficacy Amendments did not contain a separate approval process for drugs that were copies or “me-too” counterparts of previously approved drugs.⁷¹ Before these Amendments, once the FDA had approved a new drug’s NDA for safety, the FDA generally allowed “me-too” drugs—now called generics—to enter the marketplace without systematic study, so long as the generic equivalent was marketed under the same labeling as the approved drug upon which it was patterned.⁷² The reasoning behind this liberal market entry policy for generics was based on a reading of the original FDCA, which defined a “new drug” as any drug which was not generally recognized by experts as safe.⁷³ Thus, once a new drug had been approved for safety, the

⁶⁸ See *id.* at 621. In total, the NAS-NRC had evaluated approximately 16,500 claims made on behalf of the 4,000+ drugs that had been marketed pursuant to effective NDAs in 1962. Seventy percent of the claims were found not to be supported by substantial evidence of effectiveness, and only 434 drugs were found effective for all their claimed uses.

⁶⁹ See *Am. Pub. Health Ass’n v. Veneman*, 349 F. Supp. 1311, 1313–14 (D.D.C. 1972) (explaining that the process was interactive and that drug manufacturers whose drugs did not pass the test were given additional time to either amend their labels or engage in further testing and supplement the record to support a favorable efficacy determination); see also Walsh & Pyrich, *supra* note 17, at 900 n.56 (indicating that manufacturers of drugs found “probably effective” were given one year to submit efficacy data, while manufacturers of drugs found “possibly effective” were given six months to do the same).

⁷⁰ See *Veneman*, 349 F. Supp. at 1314.

⁷¹ See *supra* note 13 (defining generic or “me-too” drugs).

⁷² Richard A. Merrill, *Symposium on Regulating Medical Innovation: The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1772 (1996).

⁷³ The scientific experts’ recognition now encompasses an efficacy component, and is commonly referred to as “GRASE” or “generally recognized as safe and effective.” See *supra* note 58.

generic copy of that drug was considered to have passed the “generally recognized” standard of safety for marketing.⁷⁴

The new efficacy requirements for drug approval presented a significant challenge for the FDA because the universe of pre-1962 drugs included not only the aforementioned 4000+ previously approved innovator drugs but also nearly *ten times* as many me-too drug products that were on the market without formal FDA approval.⁷⁵ In a makeshift decision that reflected strapped resources as much as simple fairness considerations, the FDA allowed those previously marketed generic drugs to remain on the market once the FDA had granted their corresponding innovator drugs renewed efficacy approval.⁷⁶ The burden of providing the substantial evidence of efficacy rested exclusively with the innovator drug manufacturer and allowed the generic to ride on the innovator’s coattails.

This system broke down when the innovator drug failed to satisfy the new effectiveness requirement and was forced to withdraw the drug from the market. Following a series of lawsuits by pharmaceutical manufacturers, whose NDA approvals had been withdrawn for failure to show the required efficacy, the Supreme Court held that generic copies of those drugs had to withdraw from the market as well, because it would be patently unjust to exempt the generics alone from the new efficacy requirements.⁷⁷

⁷⁴ See generally Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185 (1971). Generic manufacturers either concluded independently that their products were generally recognized as safe, because an NDA was in effect for a version manufactured by another company, or else they obtained an opinion from the FDA that their drugs were not “new” but “old” drugs that were by definition already generally recognized as safe. The FDA kept no record of these “old drug” opinions, but apparently issued several thousand between 1942 and 1962. *Id.* The FDA later issued a statement of policy formally withdrawing the holdings of the “old drug” opinions in 33 Fed. Reg. 7758 (May 28, 1968). *Id.* See also 21 C.F.R. § 310.100 (2007).

⁷⁵ See Merrill, *supra* note 72, at 1772.

⁷⁶ See, e.g., Department of Health, Education, and Welfare Drugs for Human Use Containing, Quercetin, Hesperidin, or Bioflavonoids, 33 Fed. Reg. 818 (Jan. 23, 1968) (stating that the first implementation notice covered the approval of all me-too drugs for one group of drugs [bioflavonoids] with renewed efficacy approval).

⁷⁷ The Supreme Court articulated this holding in a series of four decisions, all decided on June 18, 1973. See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *Ciba Corp. v. Weinberger*, 412 U.S. 640 (1973); *Weinberger v. Bentex Pharm., Inc.*, 412 U.S. 645 (1973); *USV Pharm. Corp. v. Weinberger*, 412 U.S. 655 (1973).

Following these decisions, the FDA then announced that, going forward, it would apply the “new drug” requirements of the Drug Efficacy Amendments uniformly to all drugs, including identical, related, or similar drug products of previously approved innovator drugs.

Because the Drug Efficacy Amendments extended the definition of a new drug to require proof of both safety and effectiveness, there was uncertainty about how to review the previously marketed generic drugs that inherently did not make novel therapeutic claims.⁷⁸ The FDA realized that it would be impossible to apply the new standards to all generic drugs on a case-by-case basis, based on sheer volume alone.⁷⁹ But the Supreme Court had clearly ruled that all “new drugs” were subject to the NDA requirements, intimating that generic drug manufacturers had to perform the same or similar studies as innovator pharmaceutical manufacturers to independently prove the safety and efficacy of the generic drug.⁸⁰ The FDA, and by extension the generic drug industry, were stuck between a rock and a hard place.

Initially, generic drug companies attempted to nominally satisfy the “new drug” requirements by filing so-called “paper” NDAs, in which the generic applicant relied upon published data concerning the safety and efficacy of the previously approved drug as proof that its own, identical product was safe and effective.⁸¹ However, most of the innovator’s data were not published, were protected by trade secret law and, thus, were not readily available for most approved drug products.⁸² Therefore, in an effort to make

⁷⁸ See *Weinberger*, 412 U.S. at 650.

⁷⁹ There existed between 100,000 and 500,000 of those products, few of which the FDA had approved for safety and efficacy before marketing—the generics had merely come to the market under the same label as the innovator. *Id.*

⁸⁰ See *supra* note 74; see also Beth Understahl, *Authorized Generics: Careful Balance Undone*, 16 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 355, 361 (2005).

⁸¹ See Understahl, *supra* note 80, at 361–62.

⁸² See Merrill, *supra* note 72, at 1866 n.68. The FDA recognized that while generic drugs needed to be approved, to avoid prolonging the innovator/brand name drug’s market monopoly, approving the generics on the basis of clinical trial data supplied (and paid for) by the pharmaceutical manufacturer of the innovator drug was tantamount to appropriating its property. *Id.*

it easier for the generics to remain on the market and to avoid requiring duplicative clinical testing, while still maintaining the mandated legal consistency, the FDA devised the concept of an Abbreviated New Drug Application (“ANDA”).⁸³

ANDAs represented the first statutory attempt to regulate the generic drug industry, albeit using standards less rigorous than those used to regulate the innovator industry. The ANDA was significantly less onerous than the NDA and was initially only available for generic drug manufacturers who had copies of pre-1962 drugs on the market.⁸⁴ ANDAs did not require safety and effectiveness data as long as the copy of the innovator drug possessed the same physiological properties—bioavailability and bioequivalence—as the innovator drug.⁸⁵ The ANDA required evidence that the generic drug had the same active ingredients, bioavailability, strength and dosage form as the listed drug upon which it was patterned; that the generic was bioequivalent to the reference listed drug; and that it was made in conformity with current good manufacturing practices.⁸⁶

Despite the FDA’s best efforts, difficulties still arose with this system. Companies selling generic drugs could not even begin the abbreviated approval process until after patents on the branded drug had expired. Although the FDA had already approved the active ingredients used in the generic drugs, the generic manufacturers still needed to use the active ingredient of the innovator drug to conduct their own bioequivalence and manufacturing tests. A generic manufacturer took the risk of having a patent infringement suit filed against it by an innovator if

⁸³ Regulations governing the filing and content of ANDAs were adopted in February 1969 but were not actively practiced until the mid 1970’s. *See* Abbreviated Application, 34 Fed. Reg. 2673 (Feb. 27, 1969) (codified at 21 U.S.C. § 355 (1970)).

⁸⁴ *See* Merrill, *supra* note 72, at 1866 n.68.

⁸⁵ *See* Hoffmann-LaRoche, Inc. v. Weinberger, 425 F. Supp. 890, 892–93 (D.D.C. 1975). “Bioequivalence” meant that the active ingredient is absorbed at the same rate and to the same extent for the generic drug as for the innovator drug. “Bioavailability” meant the rate or extent to which the active ingredient in a drug becomes available to the site of drug action in the human body. *See id.* at 893 n.5.

⁸⁶ At first, labeling and manufacturing information was deemed sufficient evidence to assure the FDA that individual generic versions contained the same active ingredients as the innovator products. Later, test data was required. *See id.*

the generic began using the branded drug in tests before the drug patent expired.⁸⁷

An interim policy promulgated by the FDA attempted to mitigate this issue by implicitly allowing the introduction of generics in interstate commerce before approval of its ANDA, reasoning that the generic drug was not actually a “new drug” and therefore could be given pre-approval marketing clearance.⁸⁸ The FDA reasoned that its compliance resources were limited and should be concentrated primarily in those areas where potential health problems exist, rather than in policing the distribution of copies of approved drugs that had been found safe and effective.⁸⁹ As a result, large classes of generic drugs flooded the market with every NDA (i.e., innovator drug) approval.⁹⁰

Not surprisingly, a high profile lawsuit by the innovator pharmaceutical manufacturer Hoffmann-LaRoche called for an end to this pre-approval marketing clearance practice with some fanfare. In *Hoffmann-LaRoche, Inc. v. Weinberger*, the D.C. district court entered summary judgment for Hoffmann-LaRoche, holding that the FDA’s pre-approval marketing clearance practice was in clear violation of the FDCA’s requirements of approving a drug for safety and efficacy *before* marketing.⁹¹ It concluded that the statutory approval mandate before marketing applied even if the generic drug was the chemical equivalent of an already approved drug.⁹² In its decision, the *Hoffmann-LaRoche* court recognized the potential anticompetitive effects of the ruling, particularly with regard to the extended patent protection that would accrue to the drug company plaintiff and to other drug manufacturers with approved NDAs. However, the court sidestepped addressing these future implications, reasoning that the

⁸⁷ *See id.*

⁸⁸ *See id.*

⁸⁹ *See id.* at 892.

⁹⁰ *See id.*; *see also supra* note 72. It was estimated that in the mid-1970’s, five to thirteen such “pre-approved” generic drugs existed for every new drug that had an approved NDA. *Hoffmann*, 425 F. Supp. at 892.

⁹¹ *Id.* at 894.

⁹² *See id.* at 894–95.

overriding interest at hand was to ensure the health and safety of the public through compliance with the FDCA.⁹³

As a result of *Hoffmann-LaRoche*,⁹⁴ the late 1970's and early 1980's were halcyon years for Big Pharma—a name coined at around this time to describe pharmaceutical companies with big profits and large research and development expenditures. During that time, Big Pharma successfully kept generic drugs off the market while their innovator pharmaceutical patents, claiming the relevant branded drug products and processes of making or using them, were in force.⁹⁴ Because generic manufacturers could not even begin the appropriate bioequivalence and associated testing required for FDA approval until after the relevant patents had expired, the FDA regulations effectively extended the patent term of the brand-name drug and unduly delayed generic competition for some years after expiration of the relevant patents. As a result of the increasing dearth of generic drugs in the “monopolized” pharmaceutical marketplace, patients, as drug consumers, faced steadily increasing costs. By the early 1980's, the FDA estimated that there were approximately 150 brand-name innovator drug products whose patents had expired, yet, for which there was no generic equivalent on the market.⁹⁵

This improvident system of de facto patent term extension and, by extension, delayed generic market entry and sustained higher drug prices, provoked another generic-branded court dispute. This one, like the one before it, eventually resulted in another momentous shift in FDA law. The *Roche Products v. Bolar Pharmaceutical Co.* case involved a suit between a large

⁹³ See *id.* at 895. The court essentially forecast the legal imbroglio that would come to a head at the soon-to-be created Court of Appeals for the Federal Circuit (“Federal Circuit”). See *Roche Prods. Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984).

⁹⁴ A brand-name drug is usually “covered” by a series of patents, which can include: product patents (covering the active ingredient of the drug), process patents (covering the process of manufacturing the drug), method-of-use patents (covering a particular method of using the drug), and formulation patents (covering both the active and inactive ingredients in a drug, e.g. a final dosage form tablet or capsule).

⁹⁵ By that time, only fifteen generic equivalents had been approved for post-1962 drugs. See H.R. REP. NO. 98-857, pt. 1 at 16 (1984), as reprinted in 1984 U.S.C.A.N. 2647, 2649.

pharmaceutical company (Roche) and a manufacturer of generic drugs (Bolar).⁹⁶ Roche sought to enjoin Bolar from using its patented drug in the bioequivalence and manufacturing studies necessary to market, after expiration of the Roche patent, a generic version of Roche's branded drug Dalmane®, a sleeping pill.⁹⁷

It was perhaps not surprising that the newly-created Federal Circuit, charged with the task of unifying (and in effect strengthening) the patent system, held for patentee Roche and enjoined Bolar from beginning its FDA mandated bioequivalence tests until the patent on Roche's drug's active ingredient had expired.⁹⁸ The pro-patent *Roche* Court reasoned that such bioavailability testing constituted a prohibited infringing use of the patented drug product. The Federal Court explicitly refused to create a so-called "experimental use" exemption to United States patent laws for the testing of generic drugs, to counteract the unbalanced FDA laws, as Bolar had argued, because such "legislative activity [was] proper only for the Congress."⁹⁹

F. Generic/Innovator Forced Compromises—The Hatch-Waxman Amendments

Impelled to action by the *Roche* decision, and urged ahead by public pressure and industry lobbying, Congress swiftly passed the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the "Hatch-Waxman Amendments."¹⁰⁰ The portion of the legislation that overruled the *Roche* decision was

⁹⁶ See *Bolar Pharm. Co.*, 733 F.2d at 860.

⁹⁷ *Id.*

⁹⁸ The Federal Circuit was established in 1982 as the appellate court with nation-wide jurisdiction for all patent-related cases. The court was formed by the merger of the United States Court of Customs and Patent Appeals and the appellate division of the United States Court of Claims. See About the Federal Circuit, <http://www.fedcir.gov/about.html> (last visited Sept. 12, 2007).

⁹⁹ *Bolar Pharm. Co.*, 733 F.2d at 863–64. Generic manufacturer Bolar unsuccessfully argued that the "traditional" experimental use exception had been created at common law and deserved to be followed as a guiding (if not binding) precedent, to respect the public policy favoring generic drugs.

¹⁰⁰ Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended throughout 15, 21, 28, and 35 U.S.C.). Amendments were made to both the FDCA and the Patent Laws in an effort to engineer a statutory compromise in both areas of law. The Hatch-Waxman Amendments embody this compromise.

pushed through Congress as an addendum to a set of provisions to a patent term extension bill that had already cleared the Senate.¹⁰¹ The resulting Amendments were much broader in scope and application than the originally crafted legislation. The Hatch-Waxman Amendments served to establish a regulatory framework that afforded consumers improved access to affordable prescription drugs, while balancing the incentives for continued innovation by research-based pharmaceutical companies with opportunities for market entry by generic drug manufacturers.

The Hatch-Waxman Amendments created a statutory “safe harbor” from patent infringement, *inter alia*, to enable a generic drug manufacturer to make and use the innovator drug’s active ingredient in bioequivalence and other studies required to meet the ANDA requirements, while the innovator drug’s patent was still in force.¹⁰² The Amendments also shortened the period needed to obtain generic drug approval, by affirmatively allowing ANDA filers to rely on the safety and efficacy data compiled in the brand-name pharmaceutical manufacturer’s NDA, whether published or not.¹⁰³ At the same time, the enforceable patent term for the innovator drug could be extended to make up for patent life lost during the lengthy and expensive approval process for the innovator drug.¹⁰⁴ To achieve both objectives of this balanced compromise—regulating time did not burn patent term or allow patent extension—a set of complex procedures were established by

¹⁰¹ See Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD DRUG L.J. 188 (1999).

¹⁰² See 35 U.S.C. § 271(e)(1) (1984) (exempting from patent infringement tests and investigations conducted by the ANDA filer solely for uses “reasonably related” to generating data for obtaining FDA approval). In fact, the language of § 271(e)(1) does not restrict the “safe harbor” to generic companies and ANDA filers. It applies to any uses “reasonably related” to submission of information to the FDA. See *Merck KGaA v. Integra LifeSciences I, Ltd.*, 545 U.S. 193, 202 (2005).

¹⁰³ Compare *supra* note 82, with 21 U.S.C. § 355(j) (1984) (stipulating that ANDA filers are not required to repeat the animal and clinical testing using an already-approved drug ingredient or dosage form, as ANDAs do not contain clinical studies, but instead ANDA applicants must establish bioequivalence to the innovator drug). In general, bioequivalence data allows the ANDA filer to piggyback on the innovator drug manufacturer’s approval and safety and efficacy data, published or unpublished.

¹⁰⁴ See 35 U.S.C. § 156 (1984) (governing patent term extensions).

statute to streamline any patent infringement issues occasioned by the planned generic entry into the market.¹⁰⁵

While Hatch-Waxman endeavored to accelerate the FDA's approval of generic drugs, while preserving incentives for continued investment in new drugs, in practice, it further empowered the FDA in its regulation of the pharmaceutical industry, which now actively included innovator drug companies and generic drug companies, alongside prescribing physicians and consumers. The FDCA as amended sought to encourage greater expenditure in the area of pharmaceutical innovation, by granting longer effective patent terms while simultaneously encouraging generic drug development and ensuring greater competition in the sale of safe and effective drugs in the pharmaceutical marketplace.¹⁰⁶ Although it is an exaggeration that the Hatch-Waxman Amendments created the generic drug industry, it is indisputable that they served to greatly bolster the competitive forces surrounding generic drug entry.¹⁰⁷ With this sea change, the FDA expanded to fill the regulatory space surrounding the

¹⁰⁵ For a detailed discussion of the patent infringement issues under Hatch-Waxman, see Katherine A. Helm, *Outsourcing the Fire of Genius: The Effects of Patent Infringement Jurisprudence on Pharmaceutical Drug Development*, 17 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 153, 174–82 (2006).

¹⁰⁶ For example, the Hatch-Waxman amendments made the filing of an ANDA an act of constructive patent infringement that allowed the innovator drug manufacturer to sue the generic. It also provided for a five-year period of data exclusivity for new drug entities, i.e., the innovator drug, and a three year period for supplements requiring clinical trials, before a generic could be approved. In addition, the FDA could not approve the generic for the lesser of 30 months after the ANDA filing, patent expiration, or a court holding of patent invalidity (the “30 month stay”). This allowed the generic drug manufacturer to file an ANDA before the patent term expired while giving the innovator pharmaceutical manufacturer the chance to enforce its patents against the generic to prevent marketing before valid patent expiration. These stop gaps took some pressure off the FDA to expedite approval of generics in their attempt to promote competitive prices for safe and effective drugs. *See id.* at 173–82 & n.89. Finally, the Hatch-Waxman Amendments fostered generic entry into the market by giving the first ANDA filer a 180 day period of market exclusivity vis-à-vis other generics. This made first generic entry much more profitable. It also led to many abuses in this “balanced” system. *Id.*

¹⁰⁷ Generic drugs now comprise at least 50% of the prescriptions filed for pharmaceutical products, up from 19 percent in 1984. *See* Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, July 2002, available at www.ftc.gov/os/2002/07/genericdrugstudy.pdf; *see also supra* note 96.

seemingly incompatible goals of drug safety, efficacy, access and availability.

As this Note has tried to demonstrate, during the first half of the 20th century, Congress steadily expanded the scope and breadth of the FDA's regulatory authority to cover all aspects of drug approval, labeling and marketing, in efforts to protect public health and safety. One consequence of the regulations is that the generic drug industry has become an established part of the pharmaceutical industry. The FDA has now also taken on the role of an overarching guardian, to try and maintain the balance between the competing interests of generics and innovators as part of its public health mandate. As generic drug approval has diluted the duration of the innovator's market exclusivity and thus their time to recoup the costs of drug development and approval, much of the focus has shifted to competition and increasing regulations with regard to drug marketing. The next Part will explore the FDA's regulatory role in this area.

II. OVERSTEPPING THE BOUNDS: THE FDA'S OVERBROAD REGULATION OF DRUG ACCESS AND AVAILABILITY

As chronicled in Part I, it is indisputable that over the last century, increasingly expansive FDA regulations have increased the cost and time required to bring new drugs—and to authorize new uses of approved drugs—to market. In 1906, there was no drug pre-approval process. A century later, in a generally more competitive and risk averse climate, the process is more tightly regulated, staggeringly time-consuming, and overwhelmingly expensive. Moreover, generic drug entry is occurring earlier in the drug lifecycle, i.e., in many cases prior to patent expiration.¹⁰⁸ The

¹⁰⁸ An increasingly contentious area of litigation is the surge in pharmaceutical patent challenges mounted by ANDA applicants seeking to market generic versions of approved drugs while the patents on the approved drug or its use are still in place. Under Hatch-Waxman, ANDA filers wishing to enter the market before valid expiration of the innovator drug manufacturer's patents must include in their ANDA a "Paragraph IV certification" that the innovator's relevant patents are invalid or will not be infringed by the manufacture, use, sale or offer for sale of the generic product. 21 U.S.C. § 355(j)(2)(A)(vii)(IV). Nowadays, the lion's share of these "Paragraph IV" patent challenges are being mounted against the innovator's secondary or second-generation

overall effect of this early competition from generic drug manufacturers on pharmaceutical drug prices is titanic. It is felt by consumers, government and private healthcare insurers, hospitals, doctors, lawyers, lobbyists, and the whole of the healthcare industry. This increase in competition has directly resulted in more aggressive attempts to capture and police the pharmaceutical market.

A. The Rise of Pharmaceutical Advertising

Pharmaceutical manufacturers seeking to keep their corner on the drug market have come to realize that the dilution of the market by generic competition can be mitigated by certain factors, including the physicians' and the patients' familiarity with the branded drug as compared to a generic drug. Consequently, pharmaceutical companies have aggressively focused their major efforts on drug marketing and promotion tactics, both to prescribing physicians and to consumers. Drug manufacturers are well aware that successful promotional techniques can mold prescribing habits for the lifetime of a drug, which can, in turn, increase long term revenue and encourage investors.¹⁰⁹ In addition, major pharmaceutical companies have become increasingly sophisticated at analyzing their drug portfolios to identify potential "blockbuster" products that will be able to generate the returns needed to recoup past investments and spur future research investments, before generic competition enters the scene.¹¹⁰

patents. See generally Denise L. Loring & Katherine A. Helm, *Second Generation Pharma Patents*, N.Y.L.J. (Jan. 22, 2007), available at <http://www.ropesgray.com/secondgenerationpharmapatents/>.

¹⁰⁹ See BARRY R. FURROW ET AL., HEALTH LAW: CASES, MATERIALS AND PROBLEMS, 203 (West Group Publishing, 5th ed. 2004).

¹¹⁰ "Blockbuster" drugs are generally defined as brand-name drug products with annual gross sales of \$1 billion or more. Less than 100 drug products on the U.S. market are blockbusters. See Blockbuster Drug, Wikipedia, http://en.wikipedia.org/wiki/Blockbuster_drug (providing examples on the market today include Allegra® (Aventis), Advair® (GlaxoSmithKline), Avonex® (Biogen Idec), Duragesic® (Johnson & Johnson), Epogen® (Amgen), Fosamax® (Merck), Lipitor® (Pfizer), Nexium® (AstraZeneca), Pravachol® (Bristol-Myers Squibb) and Zyprexa® (Eli Lilly)) (last visited Sept. 12, 2007).

For decades, drug manufacturers promoted their products directly and exclusively to physicians, in an attempt to influence their prescribing habits and, in turn, consumer sales of their drugs. In the 1980's, pharmaceutical companies proposed that the FDA allow advertising directly to consumers, arguing that the public should not be denied access to the latest scientific information and knowledge.¹¹¹ Although product-claim advertisements were not barred from broadcast mediums, a tangle of thorny regulations concerning the required disclosure of product labeling information on risks and benefits made it prohibitively difficult to air television advertisements. In 1997, the pharmaceutical industry triumphed when an FDA policy change made "direct-to-consumer" (DTC) advertising feasible.¹¹² Prescription drug manufacturers responded promptly and swiftly by promoting their prescription drug products through a variety of mediums, including newspaper, magazine, television and later, internet marketing. DTC advertising quickly became a hugely successful promotional tool of drug manufacturers in the United States and elsewhere.¹¹³

To date, DTC advertisements have mostly been channeled through mass media, particularly broadcast television. In the future, DTC advertising is likely to mirror drug evolution and become more personalized, with targeted demographic profiling and messages tailored for specific patient populations. Many companies have begun promoting the use of targeted, autologous drug therapies through the concept of personalized medicine, in part response to their ostensibly waning pipelines for the large

¹¹¹ See JOHN ABRAMSON, *OVERDOSED AMERICA: THE BROKEN PROMISE OF AMERICAN MEDICINE* 150 (HarperCollins 2004).

¹¹² See Dep't of Health and Hum. Servs. et al., *Guidance for Industry: Consumer-Directed Broadcast Advertisements* (1999), available at <http://www.fda.gov/cder/guidance/1804fnl.htm>; see also Janice Hopkins Tanne, *Direct To Consumer Drug Advertising Is Billion Dollar Business in US*, 319 *BRIT. MED. J.* 805 (1999).

¹¹³ The United States, New Zealand, and Canada are, to a limited extent, the only developed countries that permit DTC advertising of prescription drugs. Europe is currently considering allowing DTC advertising for certain prescription drugs. See generally DTCA Index, <http://haiweb.org/campaign/DTCA/index.html> (last visited Sept. 12, 2007).

market “blockbuster” drugs.¹¹⁴ The personalized medicine concept is based on using genetic and other diagnostic tests to determine, before a prescription is written, how a patient will respond to a particular drug treatment and how a treatment can be individualized based on a patient’s molecular, genetic, disease, or metabolic profile.¹¹⁵ Biotechnology companies have taken a lead role in developing and promoting personalized medications, in an attempt to become major players in the healthcare market, instead of serving as mere research facilities or early stage drug developers.¹¹⁶

Since the late 1990’s, Big Pharma has worked to maintain their foothold in the healthcare market by heavily investing in DTC advertising, but also by expanding their sales forces for detailing (i.e., meeting directly with) physicians.¹¹⁷ These physician-industry interactions are rife with potential conflicts between the drug sellers and the physicians—the entry point to market.¹¹⁸

¹¹⁴ See Rex Nutting & Emre Peker, *Finally, Drug Prices Are Cooling Off: How Americans Could Save Billions of Dollars in Out-Of-Pocket Costs*, MarketWatch from Dow Jones, July 20, 2007, available at <http://www.marketwatch.com/news/story/story.aspx?guid=%7BD4B98AFA%2DD862%2D4E22%2DAD06%2D17166872504E%7D&siteid=rss> (documenting the leveling off of pharmaceutical profits, due to fewer blockbuster drugs, and assessing the pipeline of major drugs set to be approved as largely “niche” [i.e., personalized] drugs to fight cancer.)

¹¹⁵ See, e.g., Barbara J. Evans, *What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?*, 61 *FOOD & DRUG L.J.* 753 (2006).

¹¹⁶ For example, Genzyme Corporation is a biotech company that has become well known for its development of diagnostic tests to help physicians individualize treatments by predicting patient responses to targeted cancer therapies. In 2006 alone, Genzyme introduced six new personalized medicine tests across a range of cancer types. See, Overview of Genzyme Corporation, Genetics/Diagnostics, available at <http://www.genzyme.com/corp/structure/corporateoverview.asp> (last visited Sept. 12, 2007).

¹¹⁷ For a historical review of drug detailing as a promotional mechanism, see Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 *FOOD & DRUG L.J.* 309, 309–16 (1992).

¹¹⁸ The marketing practices of pharmaceutical manufacturers often include industry-sponsored gifts to physicians, in the form of drug samples, meals, conference travel, educational programs, research funding, and honoraria. Many studies have demonstrated that the sponsoring drug company’s products are favored by participating physicians. See, e.g., M.A. Bowman & D.L. Pearle, *Changes in Drug Prescribing Patterns Related to Commercial Company Funding of Continuing Medical Education*, 8 *J. CONTINUING EDUC. HEALTH PROF.* 13–20 (1988); Ashley Wazana, *Physicians and the Pharmaceutical*

Many patients do not have a high degree of literacy with regard to medical care, and thus rely on their physicians to interpret drug information. While DTC advertisements are primarily used to promote so-called pharmaceutical “brand awareness,” physician detailing is still heavily relied upon to directly secure high volumes of drug prescriptions.

In deciding when, where, and how to treat their patients, physicians not only determine their short-term treatment needs, but they also ultimately create the long-term demand for prescription drug insurance coverage.¹¹⁹ As a result, individual practitioners collectively control, directly or indirectly, the vast bulk of healthcare expenditures in the United States.¹²⁰ The collective influence of physicians has become even more prominent as total spending on prescription drugs has increased—a 54% increase since 2001, compared with a 43% increase in spending on healthcare other than drugs, according to the federal Centers for Medicare & Medicaid Services.¹²¹ In 2006, prescription drugs accounted for just over 10% of the \$2.2 trillion spent on healthcare.¹²² As long as this trend continues, physicians will continue to remain a foremost target for pharmaceutical drug company marketing campaigns.¹²³

Industry: Is a Gift Ever Just a Gift?, 55 OBSTETRICAL & GYNECOLOGICAL SURV. 483, 484 (2000).

¹¹⁹ See also Hall, *supra* note 2, at 434.

¹²⁰ Physicians control approximately two-thirds of national healthcare costs. These healthcare costs include expenditures for physician services (which, in 1997, represented approximately 20% of healthcare dollars spent or \$220 billion); hospital costs (40% or \$371 billion, the largest piece of the healthcare pie); and pharmaceutical drug prescriptions, the fastest growing expenditure (8% or \$80 billion). See Hall, *supra* note 2, at 434 (“[I]nformed estimates place 70 to 90 percent of health care expenditures within the control of individual practitioners.”); see also Agency for Healthcare Research and Quality, Center for Cost and Financing Studies, *Health Care Expenses in the U.S. Civilian Noninstitutionalized Population*, 1997. Rockville (MD), 2001. AHRQ Pub. No. 01-R086.

¹²¹ See *supra* note 114.

¹²² See *id.*

¹²³ In 2000, pharmaceutical firms spent a total of \$8.5 billion on marketing. Most of these funds were spent on physician-industry interactions. Alice LaPlante, *Marketing Directly to Physicians Reaps Higher Returns for Drug Companies*, *Stanford Graduate School of Business Marketing Research* (Aug. 2006), http://www.gsb.stanford.edu/news/research/mktg_narayanan_pharmaceuticals.shtml.

B. FDA Regulation of Pharmaceutical Advertising

As pharmaceutical manufacturers have developed more aggressive marketing tactics, the FDA has become more aggressive in exercising its regulatory authority over the various forms of drug marketing and advertising to physicians and consumers. The FDA's current authority to regulate the manufacture, sale and distribution of drugs includes sweeping oversight over the promotional labeling and advertising claims made on behalf of approved drugs.¹²⁴ By FDA mandate, a drug can only be advertised or represented for its approved purposes, i.e., for the conditions for which it has been proven safe and effective.¹²⁵ No implied claims or suggestions may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.¹²⁶ Any claim or representation made in a promotional advertisement must, therefore, be wholly consistent with the approved product labeling.¹²⁷

The FDCA broadly defines labeling as "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."¹²⁸ Indeed, the courts have long held that information need not be included with the actual drug product for it to be considered labeling.¹²⁹ Increasingly, the regulatory and judicial trend has been to construe "labeling" expansively, such that labeling now encompasses nearly every form of promotional activity, including package inserts, booklets, pamphlets, mailing pieces, bulletins, reprints of academic articles, and all other literature that supplements, explains, or is otherwise textually related to the product.¹³⁰

¹²⁴ 21 U.S.C. § 352(a), (n) (1971) (labeling and advertising, respectively).

¹²⁵ 21 C.F.R. § 201.100(d) (2001).

¹²⁶ § 201.56(a)(3) (2001).

¹²⁷ § 202(1)(e)(3)–(4) (1996).

¹²⁸ 21 U.S.C. § 321(k), (m) (2000).

¹²⁹ *See, e.g.,* *Kordel v. United States*, 335 U.S. 345, 350 (1948) (The court held that a manufacturer can be found guilty of misbranding even though the product and the labeling information were shipped separately. "The fact that [the brochures] went in a different mail was wholly irrelevant.")

¹³⁰ *See* *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998); 21 C.F.R. § 202.1(1)(2) (1997).

Likewise, although the FDCA does not define advertising *per se*, the regulations hold that all descriptive matter “issued or caused to be issued by the manufacturer, packer or distributor” are subject to the provisions of the FDCA, including advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media, such as radio, television, and telephone communication systems.¹³¹

In sum, the FDA regulates virtually any dissemination of information about a pharmaceutical product. It has effectively crafted a self-described “seamless regulatory regime” in which drug products cannot be marketed or promoted to anyone, for any use, in the absence of labeling for the FDA-approved use.¹³² Some have criticized this regulatory zeal as emboldening a ubiquitous national regulatory agency that has near limitless control over the drug industry.¹³³ Nonetheless, the FDA’s broad construction of labeling and advertising, and as a consequence, off-label drug promotion, has unquestionably become one of the hallmarks of FDA regulation.

C. FDA Regulation of Off-Label Drug Promotion

A substantial part of a drug’s market share can be derived from sales for off-label uses.¹³⁴ Off-label uses have the benefit that they are not approved by the FDA and therefore do not occasion all of the costs and delays associated with the approval process itself. Despite this lack of a need for pre-marketing approval, off-label

¹³¹ 21 C.F.R. § 202.1(1)(1) (1997).

¹³² Thomas A. Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD & DRUG L.J. 57, 62 (1996).

¹³³ See Henry I. Miller, *Failed FDA Reform*, 21 REG. 24 (1998); see also David A. Kessler & Wayne L. Pines, *The Federal Regulation of Prescription Drug Advertising and Promotion*, 264 JAMA 2409, 2410 (1990) (“The definitions of labeling and advertising taken together cover—at least in the FDA’s opinion—virtually all information-disseminating activities by or on behalf of a prescription drug manufacturer.”).

¹³⁴ See David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH INTERNAL MED. 1021, 1023 (2006) (reporting that in an estimated sample of 725 million drug treatments, a total of 150 million [21%] were being used for off-label indications, while off-label treatments comprised up to 83% of an individual drug’s use); see also Jane Henney, *Safeguarding Patient Welfare: Who’s in Charge?* 145 ANNALS INTERNAL MED. 305, 305 (Aug. 15, 2006), available at <http://www.annals.org/cgi/content/full/145/4/305>.

indications are still tightly regulated in terms of how they may be marketed and promoted. For example, any inclusion of a non-FDA approved indication on a drug product's labeling renders that product adulterated and any promotion of an off-label indication renders the product misbranded.¹³⁵ Manufacturing or introducing any such adulterated or misbranded product into interstate commerce is prohibited.¹³⁶ Thus, any promotional labeling, advertising, or distribution of a drug for an off-label use by the drug manufacturer is deemed a false or misleading representation that violates the FDCA and the corresponding FDA regulations. In this way, the FDA has retained exclusive control over the drug product's labeling and promotion and, by extension, drug profits, including those from off-label sales.¹³⁷

Not surprisingly, the FDA's regulation of labeling and off-label marketing has become a popular target for proponents of deregulation.¹³⁸ Pharmaceutical companies lament the additional costs in time and money involved in compliance with FDA drug labeling regulations and in obtaining supplemental approvals for new and often very important indications. Physicians carp about FDA restrictions on their reading materials, continuing medical education, and general scientific exchanges.¹³⁹ Many believe that off-label promotion to physicians should be largely unrestricted, given physicians' general familiarity with the FDA-approval process and ability to independently evaluate the validity of a drug

¹³⁵ 21 U.S.C. §§ 351(f)(1)(B), 352(a) (2000) (stating that a drug "shall be deemed to be misbranded . . . if its labeling is false or misleading" and a label "shall not be considered to be false or misleading . . . if the health care economic information directly relates to an indication approved . . . for such drug"); 21 C.F.R. § 201(6) (1976). This misbranding concept harkens back to the 1912 Sherley Amendment. There, false and misleading claims of therapeutic effect were prohibited. *See supra* note 20. The Drug Efficacy Amendments, on the other hand, broadened the definition of misbranding to encompass anything other than an approved use.

¹³⁶ 21 U.S.C. § 331(a)-(c), (g) (2004).

¹³⁷ The only way a drug manufacturer can legally promote a new use for an approved drug product is to request FDA permission to conduct another series of clinical trials and file SNDAs for the unapproved use and await subsequent approval before modifying their drug labels to include the new use. *See supra* Part I. E.; *see also* Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55 (D.D.C. 1998).

¹³⁸ *See* Walsh & Pyrich, *supra* note 17, at 887.

¹³⁹ *See* Henney, *supra* note 134.

manufacturer's claims.¹⁴⁰ Indeed, as noted by Third Circuit Judge Cowen, "[o]nce it is accepted that off-label uses are desirable, it is difficult to maintain that doctors should be shielded from truthful information concerning when and how to use a product for an off-label use. Patients will benefit from having their doctors informed about off-label use."¹⁴¹

The pharmaceutical industry and the medical profession each believe that the FDA's costly and time-consuming processes for validating and amending drug labeling claims impinge upon their freedoms and prevent them from keeping pace with rapidly evolving medical advances. Indeed, in its efforts to implement a regulatory system that protects the public health, the heavy hand of the FDA comes down hard on the physicians' freedom to practice medicine and the drug manufacturers' freedom of speech with regard to their drug products. As a result, regulatory efforts to restrict the promotion of off-label drug uses have generally served to ally pharmaceutical companies and physicians against the FDA.

D. Balancing Physician Autonomy, Pharmaceutical Innovation and Public Health

The FDA has no jurisdiction over physicians and has consistently maintained that it does not intend to interfere with the practice of medicine. The FDA recognizes that there are important uses of drugs that are not on the label and that once a product is approved for marketing for a specific use, the FDA does not regulate how, or for what uses, physicians may prescribe that drug.¹⁴² Indeed, the FDA has affirmed that, in certain circumstances, off-label uses of approved products are appropriate, rational, and accepted medical practice.¹⁴³ The FDA's labeling

¹⁴⁰ See *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N. D. Ill. 2003) (noting that the sophistication of the audience to whom off-label uses are promoted should be taken into account when evaluating the legitimacy of such promotion).

¹⁴¹ *In re Orthopedic Bone Screw Prod. Liab. Litig.*, 159 F.3d 817, 830-31 (3d Cir. 1998) (Cowen, J., dissenting), *rev'd*, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001).

¹⁴² See *supra* note 7.

¹⁴³ See 59 Fed. Reg. 59,820 (Nov. 18, 1994) (citing FDA Drug Bulletin 12:4-5, 1982); see also *Supplemental Indications for Approved Prescription Drugs: Before the H. Comm. on Gov't Reform and Oversight, Subcomm. on Human Resources and*

restrictions are not intended either to preclude a physician from using her best judgment in the interest of the patient, or to impose liability if she does not follow the package insert.¹⁴⁴ The true controversy emerges between what a drug manufacturer could lawfully claim that a drug does and for what condition or to which patient a physician may prescribe a drug.¹⁴⁵

This controversy came to a head in the late 1980's, when pharmaceutical manufacturers aggressively increased their support for Continuing Medical Education (CME) seminars for physicians. Several educational reports were published documenting the effects of industry sponsorship on changes in drug prescribing patterns and concerns began to emerge in the medical community about the bias inherent in the sponsored CME seminars and commercial company funding to physicians.¹⁴⁶ In response to assorted lobbying efforts, Congress conducted hearings in 1990 to investigate the impact of commercial pharmaceutical funding on physicians' prescribing behavior. It determined that, in addition to promoting "on-label" uses, the seminars were also regularly being used to promote unapproved uses for approved drug products.¹⁴⁷

In the face of these educational practices, which—for approved uses—were acknowledged as being helpful to physicians, the FDA reasserted that pharmaceutical manufacturers could not promote or suggest in any way off-label uses for their products. Physicians generally looked askance at the FDA's iron fist on this issue,

Intergovernmental Relations, 104th Cong. 57–77 (1996) (statement of Michael Friedman, Deputy Comm'r for Operations, FDA). Transcript of testimony available at <http://www.hhs.gov/asl/testify/t960912a.html>.

¹⁴⁴ Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration (Notice of Proposed Rulemaking), 37 Fed. Reg. 16503, 16504 (Dep't of Health, Educ. & Welfare, July 30, 1972). Note that liability may attach against physicians based on state tort laws, which recognize labeling as a factor to consider in determining the standard of care. See discussion *infra* notes 195–202 and accompanying text.

¹⁴⁵ Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55 (D.D.C. 1998).

¹⁴⁶ See, e.g., Bowman & Pearle, *supra* note 118 (discussing the potential mechanisms of a self-reported increase in the prescribing rates of the sponsoring drug company's calcium channel and beta blocker drug products by physicians who attended CME courses on related topics).

¹⁴⁷ See *Advertising, Marketing and Promotional Practices of the Pharmaceutical Industry, 1990; Hearing Before the S. Comm. on Labor and Human Res.*, 101st Cong. 2, 5, 8–13 (1990).

preferring the open dissemination of information concerning all beneficial uses for approved drug products.¹⁴⁸ Given the obvious financial interests of pharmaceutical manufacturers to encourage off-label uses of their drugs, however, the FDA deemed it necessary to issue detailed guidance to clarify permissible practices by manufacturers. Three such Guidance Documents addressed restrictions on promotion of off-label uses and industry-supported CME programs.¹⁴⁹ The FDA promulgated the Guidance Documents in “recognition of the generally accepted practice of off-label prescription of drugs, as well as the need for full exchange of scientific views, including discussions of unapproved uses.”¹⁵⁰

The FDA’s stated goal was to deter pharmaceutical companies from promoting their own products through unregulated avenues, e.g., by distributing textbooks and medical journal articles to healthcare professionals that referred to off-label uses. To do this, the FDA broadened the definition of a “promotional relationship” to include virtually any healthcare communication between individuals in the drug industry and healthcare professionals concerning a drug’s effectiveness and use.¹⁵¹ Little distinction was made between practices of pharmaceutical manufacturers that attempted to circumvent FDA regulations and influence off-label markets and those that attempted to simply respond to physicians’ demand for scientific information about off-label uses. In point of

¹⁴⁸ As noted by one law professor, the practical import of the FDA’s stance was debatable. On the one hand, pharmaceutical manufacturers had the resources and incentives to sponsor valuable drug education, so that individual physicians would not have to rely exclusively on their own experience in making prescribing decisions. On the other hand, the manufacturers undeniably expected a return on their investment. See Noah, *supra* note 44, at 406–07.

¹⁴⁹ See Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52,800 (Oct. 8, 1996); Guidance on Industry: Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (Dec. 3, 1997) (updating the original draft publications at 57 Fed. Reg. 56,412 (1992)).

¹⁵⁰ Elizabeth A. Weeks, *Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use Under the Food and Drug Administration Modernization Act of 1997*, 54 FOOD & DRUG L.J. 645, 648 (1999).

¹⁵¹ See 62 Fed. Reg. 64,080 (Dec. 3, 1997) (explaining that all industry-supported materials and activities should be free from the promotional influence of the supporting company).

fact, both practices could occur through the nontraditional forms of information exchange, e.g., chats over coffee, that transpire in scientific and educational activities and meetings. In efforts to demarcate the boundaries in these grey zones, the FDA gave itself the authority to police the fine line between permissible and impermissible communications about off-label use.¹⁵² By most industry accounts, these Guidance Documents pushed the regulatory envelope.¹⁵³

E. Judicial Invalidation of FDA Restrictions on Commercial Speech

In the early 1990's an industry-supported nonprofit organization named the Washington Legal Fund (WLF), filed a citizen's petition challenging the FDA's restrictions on the promotion of off-label uses for approved drugs through dissemination of article reprints and sponsorship of CME programs.¹⁵⁴ When the FDA denied the petition, the WLF turned to the district court for the District of Columbia, claiming that the FDA prohibitions violated the First Amendment rights of drug manufacturers to distribute information about off-label uses and physicians to receive the same.¹⁵⁵ A series of court cases over the next few years addressed the issue of whether the FDA had unconstitutionally interfered with drug manufacturers and physicians' First Amendment freedom in speech to communicate information about the off-label uses of drug products.

The WLF argued that the unobstructed dissemination of scientific and medical information concerning off-label treatments should be allowed, *inter alia*, because of the physicians' need to

¹⁵² See *In re Orthopedic Bone Screw Prod. Liab. Litig.*, 159 F.3d 817, 830–31 (3d Cir. 1998) (Cowen, J., dissenting), *rev'd*, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001).

¹⁵³ See Miller, *supra* note 133, at 26.

¹⁵⁴ Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Drugs and Devices: Request for Comments, 59 Fed. Reg. 59820 (Nov. 18, 1994).

¹⁵⁵ The First Amendment provides that "Congress shall make no law . . . abridging the freedom of speech." U.S. CONST. amend. I. First Amendment protections extend both to distribution and receipt of commercial speech. See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 62–65 (D.D.C. 1998).

obtain reliable information about the products they prescribe.¹⁵⁶ The argument evolved into a general criticism of the FDA's practice of penalizing the pharmaceutical manufacturer as the source of the information, i.e., the "speaker" of the speech under First Amendment law. The bottom line of the argument was that because the dissemination or exchange of legitimate scientific information from or between independent sources was constitutionally sanctioned, the FDA should not be permitted to restrict the flow of such information merely because it came from a drug manufacturer.¹⁵⁷

Throughout the litigations, the FDA maintained that its approach to regulating product information was inherently congruent with its mission to promote health and safety. The FDA acknowledged that its policies prevented manufacturers from financing CME seminars and from distributing reprints of peer-reviewed journal articles that addressed off-label uses. The FDA advanced two specific interests in support of its restrictions. First, the FDA claimed it had the duty to ensure that physicians receive accurate and unbiased information so that they can make informed prescribing choices. Second, the FDA claimed it had the duty to provide pharmaceutical manufacturers with ample incentive to apply for and get new uses approved "on label," by filing SNDAs.¹⁵⁸

The D.C. Court concluded that the FDA's first interest was inadequate to justify its intrusion on free speech but the second interest was substantial.¹⁵⁹ On the whole, the court held the FDA policies more extensive than necessary to serve the government's interests and held the Guidance Documents to be an

¹⁵⁶ *Friedman*, 13 F. Supp. 2d at 56.

¹⁵⁷ *Id.* at 68 (observing that claims are not inherently misleading merely because they were neither made by scientists or academics nor evaluated by the FDA). *See also* Wash. Legal Found. v. Henney, 56 F. Supp. 2d 81, 85 (D.D.C. 1999), *vacated*, 202 F.3d 331 (D.C. Cir. 2000) ("Even under the degree of scrutiny that we have applied in commercial speech cases, decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment.") (citing *Greater New Orleans Broad. Assoc. v. United States*, 527 U.S. 173, 194 (1999)).

¹⁵⁸ *Friedman*, 13 F. Supp. 2d at 69.

¹⁵⁹ *Id.* at 71.

unconstitutional infringement of commercial speech.¹⁶⁰ In so holding, the court maintained a clear distinction between claims advanced by a manufacturer to promote its product (not allowed) and scientific conclusions published in a peer-reviewed journal or presented by a physician at a CME seminar (allowed).¹⁶¹ The court enjoined the FDA from applying or enforcing its Guidance Documents and dryly observed that the FDA should not feel responsible for ensuring that all scientific publications are unbiased and non-misleading.¹⁶²

Against the backdrop of the court mandate, the Food and Drug Administration Modernization Act of 1997 (“FDAMA”) was passed.¹⁶³ The FDAMA provided a revised framework for limited FDA supervision of the production and dissemination of select materials concerning off-label drug use to physicians and other members of the healthcare by or on behalf of drug manufacturers. In notable distinction from the earlier Guidance Documents, the statute permitted the dissemination so-called “enduring materials,” i.e., unedited reprints or copies of peer-reviewed scientific or medical journal publications, as long as the drug manufacturer had satisfied certain criteria, including having filed an SNDA on the new indication; having directly sponsored the trials; having filed the report intended for distribution with the FDA in advance; and having the reports bear the disclaimer that the new use had not been approved by the FDA.¹⁶⁴

Based on this new law, the FDA asked the district court to explicitly confine its earlier injunction to the pre-FDAMA Guidance Documents. This motion was denied in *Washington*

¹⁶⁰ *Id.* at 74.

¹⁶¹ *Id.* at 67.

¹⁶² *Id.* (“In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.”).

¹⁶³ The Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

¹⁶⁴ *See* 21 U.S.C. § 551(b) (2005). The statute also directly addressed some physician concerns by stating that no provision barred a manufacturer from disseminating information in response to an unsolicited request from a healthcare practitioner. *See id.* § 557(a).

*Legal Foundation v. Friedman*¹⁶⁵ and a subsequent opinion declared the FDAMA provisions unconstitutional.¹⁶⁶

The latter decision was appealed and ultimately vacated by *Washington Legal Foundation v. Henney*,¹⁶⁷ however, based on the FDA's novel interpretation of the FDAMA provisions and the 1997 Guidance Document. For the first time, at the appellate oral argument, the FDA recognized that a "safe harbor" existed for industry-supported scientific and educational activities and qualifying CME programs.¹⁶⁸ This late-breaking safe harbor from the FDA regulation space was unsupported by the statutory language in the FDAMA or elsewhere. Nonetheless, the FDA effectively represented to the court it would not use obvious violations of the FDAMA or the Guidelines to prosecute drug manufacturers exercising their First Amendment rights.¹⁶⁹ As a result, the D.C. Court dismissed the appeal for the technical lack of a constitutional controversy, all the while noting that it did not criticize the reasoning or conclusions of the district court.¹⁷⁰ The peculiar set of facts surrounding the appeal undoubtedly reflected the mounting pressure by various interest groups on the FDA to recognize the educational need to disseminate reliable scientific information on off-label uses.

As might have been expected, any lasting practical utility of the FDA-created safe harbor is questionable. The boundaries on commercial speech concerning drug information continue to expand and contract as the FDA struggles to formulate restrictions that will not conflict with constitutional freedoms yet will effect its perceived mandate of regulating off-label uses.¹⁷¹ At present, a

¹⁶⁵ 36 F. Supp. 2d 16, 18 (D.D.C. 1999).

¹⁶⁶ *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999).

¹⁶⁷ 202 F.3d 331 (D.C. Cir. 2000).

¹⁶⁸ *Henney*, 202 F.3d at 335. The FDA interpreted the guidelines on disseminating information on new uses, found in § 401 of the FDAMA, as forming the implied basis for a safe harbor. *Id.*

¹⁶⁹ The FDA assured the court that certain forms of conduct "would not be used against manufacturers in misbranding and 'intended use' enforcement actions based on pre-existing legislative authority." *Id.* *But cf., infra* Part III: Manufacturer Liability Resulting from Off-Label Use (discussion of current-day enforcement actions).

¹⁷⁰ *Henney*, 202 F.3d at 337.

¹⁷¹ First Amendment case law is controlling, and virtually no mention has been made in the courts of the FDA's safe harbor. *See, e.g.,* *Thompson v. W. States Med. Ctr.*, 535 U.S.

drug manufacturer can disseminate information concerning off-label drug use that appears in independent and peer-reviewed sources to members of the healthcare community.¹⁷² Solid guidance, however, is still lacking on the promotional restrictions for materials that are openly distributed by drug manufacturers to the public at large. The FDA is likely to view materials that are broadly “consumed” by the public as advertising and subject to strict regulation by the FDCA. Indeed, a tenuous distinction exists between the promotional practices of pharmaceutical manufacturers that attempt to circumvent FDA regulations and influence off-label prescribing of medications and those practices that attempt to educate physicians and to exchange scientific information in an unbiased manner. Like a teeter-totter, as FDA regulations on drug promotion and information dissemination of off-label uses fall, concerted regulatory attempts to monitor drug safety will inevitably rise.¹⁷³

The legality of off-label drug promotion is one that has frequently tested the judiciary’s ability to provide appropriate boundaries for the exercise of FDA regulatory power, for the good of the consumer, the physician and the drug manufacturer. The final Part of this Note examines the various policy considerations

357 (U.S. 2002) (holding FDA restrictions on pharmacist promotion of individually mixed “compounded” drugs an unconstitutional violation of commercial speech). *Cf.* *Sanofi-Aventis U.S. LLC v. Novo Nordisk, Inc.*, 2006 U.S. Dist. LEXIS 69150 at *35 (D.N.J. June 23, 2006) (failing to consider a safe harbor which exempts certain drug correspondence from regulation as promotional communications because it is not supported by any statute or cited any regulation promulgated by the FDA).

¹⁷² 21 C.F.R. § 312.7(a) (2002) provides a “scientific exchange” exception to drug marketing activities at, stating that promotional restrictions are not intended to impede the “full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.” This exception has led to a general practice among pharmaceutical manufacturers of separating sales personnel from “scientific exchange” personnel.

¹⁷³ Recently, some pharmaceutical manufacturers have responded by shifting their company resources away from sales and towards increased drug research and safety monitoring. Pfizer, for example, has undergone significant restructuring that involved laying off 20% of their sales force in the U.S., due in part to doctor complaints of being overrun by too many sales representatives. *See* Alex Berenson, *New Chief at Pfizer Will Reduce Sales Force*, N.Y. TIMES, Nov. 29, 2006, available at <http://www.nytimes.com/2006/11/29/business/29pfizer.html?ref=business>. Compare this trend with recent legislative proposals to increase drug safety, *infra* Part III: Proposals for FDA Reform.

surrounding the safe harbor under which physicians and pharmaceutical manufacturers can operate to develop and distribute drugs and provide advanced, state of the art medical care.

III. POLICY CONSIDERATIONS: CAN THE FDA CATCH UP TO THE FUTURE?

Because the FDA has responsibility in matters which directly and literally affect the nation's health and welfare, it is one of the most important of all Federal regulatory agencies. Its enforcement stance must be well balanced, but nevertheless effective. A timid approach can vitiate whatever protection the Congress has created for the consumer. On the other hand, an overly zealous approach can ruin a drug manufacturer by destroying public confidence in its products.¹⁷⁴

As with any deregulated activity, off-label decision-making is inherently vulnerable to unethical practices, by pharmaceutical manufacturers and others. From a physician's perspective, medical ethics control medical practice. From a drug industry perspective, legal and corporate ethics control behavior. For everyone, these professional ethics are often seen as a constraint, like the law.¹⁷⁵ While all ethics are ultimately justified by morality, professional ethics are often constrained by rules promulgated by a regulatory agency, such as the FDA. Ideally, this regulatory body is tailored to take into account, in its rulemaking, facts about the institutions involved and their respective roles in the industry.¹⁷⁶ The challenge for most regulatory bodies is to engineer and effectuate an acceptable balance between the interests of consumers and various stakeholders. In the FDA's case, the goals and interests of the parties involved in the healthcare industry are often at odds.

¹⁷⁴ American Public Health Ass'n. v. Veneman, 349 F. Supp. 1311, 1317 (D.D.C. 1972).

¹⁷⁵ See Jonathan Baron, *Do No Harm*, in CODES OF CONDUCT: BEHAVIORAL RESEARCH INTO BUSINESS ETHICS, 197-213 (D. M. Messick & A. E. Tenbrunsel eds., 1997) available at <http://www.sas.upenn.edu/~baron/chicago.html>.

¹⁷⁶ *Id.* at 197 n.2.

Patients, physicians and drug manufacturers all want to benefit from having improved drug access and availability, but they also all want to know and expect the drugs to be safe and effective. The FDA has the obligation to try and balance these potentially incompatible goals, while minimizing the industry costs of compliance.¹⁷⁷

A. *The Double-Edged Sword of Drug Regulation*

As was illustrated by the complexity of the WLF litigations, difficult and subtle balancing is called for in evaluating the FDA's role in regulating the promotion and practice of off-label drug use. Striking a proper regulatory balance between competing principles in this arena is a constant tension that becomes intensified when the players engage in diverging practices, to accomplish the same end goal of achieving public health and safety. The path to this goal intrinsically affects the outcome and each step carries the potential for both large profits and large losses. For example, a blanket prohibition on off-label drug promotion, intended to safeguard the public from unsafe and ineffective drugs, could in operation have a directly negative impact on public health. While a drug approved for one use is undergoing the FDA's stringent and time consuming review for safety and effectiveness for another use, it cannot be promoted for that new use and patients who might have received some health benefit from it suffer.¹⁷⁸

In such instances, the physician's interest and duty to treat his or her patient should supplant the government's interest in safeguarding individual patient welfare by allowing only approved drugs and uses to be marketed. This is particularly true because the FDA has already approved the drug as *safe* for all uses. Accordingly, the physician should be able to exercise his or her

¹⁷⁷ See Gardiner Harris, *Potentially Incompatible Goals at F.D.A.*, N.Y. TIMES, June 11, 2007, available at <http://www.nytimes.com/2007/06/11/washington/11fda.html> (observing that “[s]afety and speed are the yin and yang of drug regulation”).

¹⁷⁸ See, e.g., Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93 (1999) (generally discussing how the FDA should adopt an under-conservative approach towards drug approvals for new uses in AIDS treatments because of the immediate social need for life-saving treatment options).

professional autonomy to prescribe a drug for uses, or in treatments, regimens, or patient populations, that are not listed on the FDA-approved label but may nonetheless prove effective for that prescribed purpose. The physician rationale for supporting off-label use is frequently one of sheer necessity—some patients need the treatment option even if there does not yet exist enough data to demonstrate clinical effectiveness and support FDA approval for the use.¹⁷⁹ As the Supreme Court has pragmatically observed, the “off-label usage of [drugs and medical devices] is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.”¹⁸⁰

From a pharmaceutical industry perspective, however, once a drug is approved for a first use, off-label sales expand, sometimes by many multiples.¹⁸¹ This market fact encourages manufacturers to seek FDA approval only for the narrowest, most easy to support indications and then reap the benefits of off-label sales. The existing market for the drug, both on and off-label, necessarily dampens the incentives of drug manufacturers to invest the substantial time and resources necessary to conduct further trials and to develop the evidence required for FDA approval of additional uses. This marketplace deterrent is further reinforced by the Supreme Court’s holding that the FDA’s approval requirement is not subject to exception based on the difficulty or cost of obtaining approval or of the conceded benefits of the unapproved uses.¹⁸²

Early entry of generic competition also makes the pharmaceutical manufacturer much less likely to seek approval for the new use. Once a generic enters the market for a first use, it will be prescribed for all uses—on or off label. State substitution

¹⁷⁹ *Id.* at 97–98. See also Henney, *supra* note 134, at 305; Glenn C. Smith, *Avoiding Awkward Alchemy—In the Off-Label Drug Context and Beyond: Fully-Protected Independent Research Should not Transmogrify Into Mere Commercial Speech Just Because Product Manufacturers Distribute It*, 34 WAKE FOREST L. REV. 963, 971 (1999) (explaining that off-label prescribing is particularly important in certain specialties, such as cancer treatment and pediatric medicine).

¹⁸⁰ *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001).

¹⁸¹ See Radley, *supra* note 134, at 1023–24 (Tables 1 and 2).

¹⁸² *United States v. Rutherford*, 442 U.S. 544, 557–58 (1979).

laws generally require physicians to prescribe, and pharmacists to distribute, any available generic version of a drug, for all approved and unapproved uses for which it is prescribed.¹⁸³ Many of these state substitution laws also preclude medical insurers from declining to reimburse for generics prescribed off-label solely because they are unapproved for such indications.¹⁸⁴

In addition, Federal Medicare coverage policies now include, as eligible for coverage, those off-label uses that are deemed medically acceptable.¹⁸⁵ At least one court has also recently supported Medicaid reimbursement claims for certain off-label uses of approved medications that were deemed medically accepted indications.¹⁸⁶ Were a drug manufacturer to have invested in obtaining an SNDA for a new use, the market for that use would already have been viable for coverage when generic entry began. Because the same situation applies if the manufacturer did not obtain approval for the new use, there is little reason to do it. In sum, off-label uses are highly profitable for pharmaceutical manufacturers prior to generic entry, and are highly profitable for generic drug manufacturers thereafter.

¹⁸³ See, e.g., N.Y. Educ. Law § 6810(6)(a) (2002) (requiring all prescriptions to include the language that “this prescription will be filled generically” unless certain limited exemptions apply to allow it to be dispensed as written).

¹⁸⁴ Local coverage determinations are made by the relevant state authorities. See, e.g., Tenn. Code Ann. § 56-7-2352(a)(6)–(7), (c)(1), cited in *Richardson v. Miller*, 44 S.W.3d 1, 14 (Tenn. Ct. App. 2000).

¹⁸⁵ For example, coverage is available for the off-label uses of drugs in numerous anticancer chemotherapeutic regimens. See, e.g., Centers for Medicare & Medicaid Services: Off-Label Use of Colorectal Cancer Drugs Allowed in Select Clinical Trials, 1 J. ONCOLOGY PRACTICE 12–14 (2005). All national coverage determinations are made by the Centers for Medicare and Medicaid Services (CMS). See also Social Security Act, § 1861(t)(1); Medicare Benefit Policy Manual (CMS Pub. 100-2), Chap. 15, § 50.4.2 (defining medically acceptable as being supported by certain compendia and authoritative medical literature and/or accepted standards of medical practice). See generally CMS Medicare Coverage Database, <http://www.cms.hhs.gov/mcd/indexes.asp> (last visited Sept. 12, 2007).

¹⁸⁶ See *Edmonds v. Levine*, 417 F. Supp. 2d 1323, 1343 (D. Fla. 2006) (overruling a state policy that denied reimbursements under Medicaid for off-label uses of Neurontin®). *But cf.*, *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 39, 51–53 (D. Mass. 2001); *supra* text accompanying notes 214–218 (discussing Parke-Davis liability under False Claims Act for causing the submission of fraudulent claims to the government for off-label uses of Neurontin® that were ineligible for reimbursement under Medicaid).

The problem that emerges is the ensuing dearth of scientific evidence of efficacy available for physicians to assess and evaluate off-label treatments.¹⁸⁷ Pharmaceutical companies are insufficiently motivated to invest in detailed and controlled supplementary clinical research if off-label uses are already profitable and the costs associated with the development and licensure to get such uses formally approved may not be recoverable, because of generic drug entry. Branded pharmaceutical manufacturers have tried recovering their lost market share from generic drug manufacturers by suing the generic manufacturers for inducing patent infringement of the branded company's patented new uses for the drug.¹⁸⁸ However, courts have held that pharmaceutical companies as "new use" patent holders cannot sue a generic drug maker for inducing infringement if the patented use is off-label, i.e., not FDA approved.¹⁸⁹ Under this jurisprudence, incentives for pharmaceutical manufacturers to further develop drugs that have generic competition (i.e., drugs that are off-patent or near off-patent) are thoroughly dismantled.¹⁹⁰

Despite the good intentions of the FDA to regulate drug labeling and off-label drug promotion, therefore, it seems clear that any administrative policy will necessarily have some reverberating negative effects on modern medical practice. Overbroad

¹⁸⁷ See Henney, *supra* note 134, at 305–07.

¹⁸⁸ In such cases, pharmaceutical manufacturers have argued that generics should not be allowed to obtain FDA approval on one use and then benefit from the state laws that substitute generic drugs for all indications for which the brand name drug is used, including methods of using the drug that are patented by the branded pharmaceutical manufacturer. The pharmaceutical manufacturers lost. See *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1354–62 (Fed. Cir. 2003); *Allergan, Inc. v. Alcon Labs.*, 324 F.3d 1322, 1330–34 (Fed. Cir. 2003), *cert. denied*, 2003 U.S. LEXIS 8602 (Dec. 1, 2003).

¹⁸⁹ This is so even if the generic manufacturer is aware of the future probability of crossover prescriptions and sales of their drug for the off-label uses. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d at 1355, 1365 (evidence of a generic company's reliance on financial projections that demonstrate its drug will be prescribed in a manner that would infringe a method patent is insufficient to show the generic manufacturer encouraged or promoted doctors to prescribe the drug in that manner). *Accord Allergan*, 324 F.3d at 1334.

¹⁹⁰ For a further discussion of the issues, see Rebecca Eisenberg, *Pharmaceutical Innovation and Cost: An American Dilemma: The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717 (2005).

restrictions can unduly hamper physicians' freedoms to learn about and make personal medical judgments and drug manufacturers' rights to discuss their products with the medical community. On the other hand, unfettered practices may remove incentives to support the development of real, controlled data on the efficacy of drugs for new indications. Absent adequate incentives for drug manufacturers to generate and disseminate information about the range of available therapeutics to health care professionals, physicians risk, in turn, making determinations about the relative safety and effectiveness of their treatment options that is wide of the mark. The double-edged sword of drug regulation can cut deeply both ways.

Good decisions are made with as much data as possible. Good healthcare decisions likewise should be made with as much data on the use of drugs for non-approved indications as possible. The FDA requires the data to safeguard the public, the physician wants the comfort of the data when prescribing drugs and the manufacturer wants to be able to truly market the data and profit from the drug's new indication for a substantial enough period of time to recoup the costs of testing and to earn a profit. The time taken for the FDA's regulatory machinery to approve new indications plainly lags behind the state-of-the-art medical practice. At the same time, the undesirable promotion of unevaluated or under evaluated off-label indications is costly to the pharmaceutical manufacturer and to the healthcare system as a whole. On some level, the drug industry needs the FDA's regulatory framework as much as the FDA needs the drug industry to adhere to it. But where does this leave the physician?

B. Medical Liability Resulting From Off-Label Use

The FDA makes clear that it does not regulate the practice of medicine and that physicians will not be held liable, under the FDCA, for damage caused by a drug used off-label.¹⁹¹ Physicians are by no means exempt from the risk of liability arising from off-label prescribing, however. The fear of liability arising under state tort law, including products liability and medical malpractice laws,

¹⁹¹ See *supra* note 7.

generally serves to keep physicians' off-label prescribing practices in check.

In the case of products liability law, if a patient is injured by a drug product and files a claim against the drug manufacturer and the prescribing physician, the "learned intermediary doctrine" can affect the apportionment of liability between the defendants. This doctrine is based on the presumption that physicians, as learned intermediaries between drug manufacturers and patients, are responsible for warning patients of the potential hazards and defects associated with prescribed medications.¹⁹² The drug manufacturer is excused, therefore, from warning each patient who receives the product so long as the manufacturer properly warns the prescribing physician of the product's dangers.¹⁹³

Drug manufacturers typically use the learned intermediary doctrine as an affirmative defense against liability, thereby shifting blame for the patient's injuries to the prescribing physician. The determination of liability under this doctrine generally hinges on the whether the risk of harm was foreseeable by the manufacturer (unforeseeability of the off-label use or non-conveyance of the physician's warning to the patient limits the manufacturer's liability) or whether the off-label use is the known standard of care in the medical community (common usage by the profession limits the physician's liability). Thus, while physicians are not required to disclose to patients that a drug is being prescribed for off-label use, most physicians make efforts to limit their liability by doing so.

While the learned intermediary doctrine can technically be invoked each time a prescription is written, the practical strength of the doctrine may have diminished over the years, as physicians tend to stand less as intermediaries between their patients and drug

¹⁹² The roots of the doctrine originated in *Marcus v. Specific Pharms. Inc.*, 77 N.Y.S.2d 508, 509-10 (N.Y. App. Term. 1948).

¹⁹³ See *Crisostomo v. Stanley*, 857 F.2d 1146, 1152 n.17 (7th Cir. 1988); accord *Kirk v. Michael Reese Hosp. & Med. Center*, 513 N.E.2d 387, 390 (Ill. 1987) (explaining how drug manufacturers typically communicate warnings relating to prescription drugs to the medical profession through package inserts, the Physician's Desk Reference, "Dear Doctor" letters, detailing, and other measures)

manufacturers.¹⁹⁴ In cases of off-label prescribing, manufacturers have attempted to benefit from the doctrine's protection by claiming that the absence of appropriate labeling constituted a sufficient warning against a drug's off-label use. This defense has met with limited success, as DTC advertising tends to undercut the rationale behind the doctrine.¹⁹⁵ Some courts have reasoned that because drug manufacturers generate a sense of product quality through mass advertising and marketing practices, they are reasonably subject to the common law duty to warn to the consumer.¹⁹⁶ However, the majority of states continue to uphold that the learned intermediary doctrine, on the general reasoning that the physician is still in the best position to evaluate the warnings put out by drug manufacturers.¹⁹⁷

¹⁹⁴ Shortly after DTC advertising was introduced, several courts rejected the learned intermediary doctrine in cases involving oral contraceptives. Each court reasoned that consumers of oral contraceptives actively choose to take the drug and prescribing physicians play relatively passive roles, therefore the doctrine does not apply and drug manufacturers must provide adequate warnings to consumers directly. *See* *Odgers v. Ortho Pharms. Corp.*, 609 F. Supp. 867 (E.D. Mich. 1985); *Stephens v. G.D. Searle & Co.*, 602 F. Supp. 379 (E.D. Mich. 1985); *MacDonald v. Ortho Pharms*, 475 N.E.2d 65, *cert. denied* 474 U.S. 920 (1985); *see also* *Hill v. Searle Labs.*, 884 F.2d 1064, 1070 (8th Cir. 1989) (extending the exception to other forms of birth control [prescription intra-uterine devices (IUD)] where prescribing physicians did not make an intervening, individualized medical judgment in the decision). Note that not all courts have adopted such exceptions, however. *See, e.g., Terhune v. A.H. Robins Co.*, 577 P.2d 975, 978 (Wash. 1978); *Martin v. Ortho Pharmaceutical Corp.*, 661 N.E.2d 352, 356–57 (Ill. 1996); *In re Norplant Contraceptive Products Litg.*, 165 F.3d 374, 379 (5th Cir. 1999).

¹⁹⁵ Indeed, the duty for pharmaceutical manufacturers to warn the patient directly is supported by the Restatement (Third) of Torts: Products Liability § 6(c)–(d) (1998).

¹⁹⁶ *See, e.g., Perez v. Wyeth Labs. Inc.*, 734 A.2d 1245, 1255–57 (N.J. 1999) (rejecting the doctrine and holding the manufacturer liable for consumer claims if its advertisements failed to provide adequate warnings); *W. Va. ex rel. Johnson & Johnson Corp v. Honorable Mark A. Karl*, 2007 W. Va. LEXIS 57, at *51–53 (W. Va. June 27, 2007) (rejecting doctrine and holding that drug manufacturers have the same duty to warn consumers about the risks of their products as other manufacturers).

¹⁹⁷ These courts still require that proper warnings be given to the physician, of course. *See, e.g., Larkin v. Pfizer, Inc.*, 153 S.W.3d 758, 763 (Ky. 2004) (“The entire system of drug distribution in America is set up so as to place the responsibility of distribution and use upon professional people.”); *accord* *McCombs v. Synthes (U.S.A.)*, 587 S.E.2d 594, 595 (Ga. 2003); *Vitanza v. Upjohn Co.*, 778 A.2d 829, 836–38 (Conn. 2001); *Pittman v. Upjohn Co.*, 890 S.W.2d 425, 429 (Tenn. 1994); *Coyle v. Richardson-Merrell, Inc.*, 584 A.2d 1383, 1385 (Pa. 1991); *White v. Wyeth Labs., Inc.*, 533 N.E.2d 748, 755 (Ohio 1988).

Off-label prescribing could also constitute medical malpractice under state law, if such prescribing was not customarily followed by physicians. In order for a medical malpractice claim to succeed on these grounds, the plaintiff must demonstrate the existence of a direct physician-patient relationship and that the physician significantly departed from the standard of care of a reasonable physician.¹⁹⁸ Because the former is generally much easier to prove, most litigations hinge on whether the physician's prescription of the drug for an off-label use was warranted, i.e., whether it was based on sound scientific evidence and sound medical opinion.¹⁹⁹

Whereas courts once held doctors to a standard of care based loosely on custom among local practitioners, nowadays the standard is more stringent.²⁰⁰ Peer-reviewed medical journals are generally considered the only reliable source of sound scientific and medical opinion, as introduced by expert testimony or as a learned treatise.²⁰¹ Some courts have held the off-label nature of the prescription itself is a factor to be considered in establishing

¹⁹⁸ Common law negligence principles dictate that a plaintiff must establish that a duty of care arose from the relationship between the plaintiff and the defendant and that the defendant breached his or her duty by failing to comply with the reasonable person standard. See VICTOR E. SCHWARTZ ET AL., PROSSER, WADE AND SCHWARTZ'S TORTS: CASES AND MATERIALS 193-95 (Foundation Press, 10th ed. 2000) (1951).

¹⁹⁹ Jacqueline M. Melonas, *Preventing and Reducing Professional Liability Risk Related to Psychopharmacology*, 23 PSYCHIATRIC TIMES (Dec. 2005), available at <http://www.psychiatrictimes.com/showArticle.jhtml?articleId=175803689>; see also *McKinney v. Schlatter*, 692 N.E.2d 1045, 1047-48 (Ohio Ct. App. 1997) (holding that a physician-patient relationship broadly arises out of a contract of employment, express or implied, where a patient seeks medical assistance and a physician agrees to render treatment).

²⁰⁰ The old custom was also based on the locality of the physician, assuming that rural customs would differ from customs in state-of-the-art urban medical centers. This community practice distinction has largely been dropped in favor of a national standard of care. See, e.g., *Brune v. Belinkoff*, 235 N.E.2d 793, 798 (Mass. 1968) ("The time has come when the medical profession should no longer be Balkanized by the application of varying geographic standards in malpractice cases."), cited in Noah, *supra* note 44, at 457 n.376.

²⁰¹ The Federal Rules of Evidence provide for a "learned treatise" hearsay exception to allow a textbook or journal article to speak for itself in court if it is recognized to be a reliable authority (as established by expert testimony or judicial notice). See FED. R. EVID. 803(18).

the reasonable standard of care (or a deviation therefrom).²⁰² Ultimately, expert testimony will be required to establish whether a specific off-label treatment demonstrates a lack of skill or knowledge, or a failure to exercise reasonable care, on behalf of the physician.²⁰³

Increasingly, and in spite of the many land mines surrounding the practice, many courts have recognized the legitimacy of off-label prescribing when it constitutes the standard of reasonable care.²⁰⁴ Even with this judicial recognition, however, many physicians remain uncomfortable with the liability risk that surrounds off-label prescribing.²⁰⁵ While it is always true that physicians must take steps to educate themselves about how to diagnose and treat new and evolving medical conditions, the burden of self-education increases with regard to learning about unapproved uses for approved drugs. Because of FDA restrictions on manufacturer-sponsored physician education about off-label uses, medical professionals do not always have ready access to the necessary information about the customary use of drugs prescribed off-label. This lack of information makes it more difficult for a prescribing physician to assess how their peers would act in treating patients. Understandably, physicians have shown tepid support for FDA regulations that cabin their ability to assess their

²⁰² In *Richardson v. Miller*, 44 S.W.3d 1, 17 (Tenn. Ct. App. 2000), the court held the exclusion of off-label use evidence to be an error of law that hampered the patient plaintiff's ability to prove her malpractice and products liability claims. In so holding, the court noted that while proof of a departure from the drug's labeling will not *ipso facto* prove a breach of the standard of care, the labeling can provide significant assistance in identifying the standard of care.

²⁰³ *Id.*; see also *Halligan v. Cotton*, 227 N.W.2d 10, 12–13 (Neb. 1975) (“[W]hether a specific manner of treatment or exercise of skill by a physician or surgeon demonstrates a lack of skill or knowledge or a failure to exercise reasonable care is a matter that must usually be proved by expert testimony.”)

²⁰⁴ See, e.g., *Klein v. Biscup*, 673 N.E.2d 225, 231 (Ohio Ct. App. 1996); *Femrite v. Abbott Northwestern Hosp.*, 568 N.W.2d 535, 541 (Minn. Ct. App. 1997); *Alvarez v. Smith*, 714 So. 2d 652, 653–54 (Fla. Dist. Ct. App. 1998); *Southard v. Temple Univ. Hosp.*, 731 A.2d 603, 611 (Pa. Super. Ct. 1999).

²⁰⁵ See, e.g., *Richardson*, 44 S.W. 3d at 10–13 (observing that physicians who prescribe off-label have a responsibility to be well-informed about the drug and, in the absence of the information found in the FDA-approved labeling, physicians bear the additional burden of obtaining reliable, up-to-date information from other sources).

own risk of professional liability for choosing to prescribe drugs off-label.²⁰⁶

C. *Manufacturer Liability Resulting From Off-Label Use*

Where there's money, there's action. Pharmaceutical manufacturers can be subject to both civil and criminal liability, under both state and federal law, where a cornucopia of claims can be brought by the public sector, private sector interest groups, private citizens on behalf of the government, or private citizens as individuals, for alleged damage caused by off-label drug use. Efforts to manage the liability risks arising from the promotion of off-label uses for a drug product by its manufacturer is akin to herding cats.

To begin somewhere, products liability law can serve to inform a drug manufacturer about the proper (and improper) practices of drug labeling and promotion. A patient's product liability claim against a drug manufacturer will be subject to strict liability in cases where the learned intermediary doctrine does not apply. As explained in the foregoing section, strict liability may apply when mass advertising and DTC marketing practices are involved, when little physician input is needed to make the medical decision, or when the drug manufacturer has given inadequate warnings to the prescribing physician.²⁰⁷ Under such circumstances, a patient will likely recover if he or she can demonstrate that the drug was unreasonably dangerous for use in the off-label treatment, because the drug manufacturer failed to directly warn the consumer of the drug's dangerous propensities. A patient may also recover even where the direct warning to the consumer was adequate, i.e., as present on the drug product's labeling, but thereafter became diluted or even vitiated by a manufacturer's over promotion of the

²⁰⁶ Such resistance likely stems from the differences in legal versus medical approaches to decision making, which are often summarized as adversarial versus scientific methods. Understandably, many physicians are unwilling to relinquish their clinical authority to non-medical parties, especially to lawmakers sitting in judgment (prospectively or retrospectively) of clinical decisions. See Peter D. Jacobson & M. Gregg Bloche, *Improving Relations Between Attorneys and Physicians*, 294 JAMA, 2083, 2083–85 (2005).

²⁰⁷ See *supra* notes 191–94 and accompanying text.

drug.²⁰⁸ Any promotion about a drug's off-label effectiveness to the end user, therefore, could make the drug manufacturer liable for any damage caused by the drug in the off-label use.

Tort liability for pharmaceutical manufacturers promoting off-label uses can also stem from a variety of negligence claims, e.g., failing to seek FDA approval of the marketed off-label use, improper labeling, promotion of an off-label use of an FDA approved drug, fraud based on the alleged misbranding, and fraud upon the FDA.²⁰⁹ Fraud actions have also been brought against drug manufacturers by individual states under various consumer fraud laws. For example, in 2004, the New York Attorney General brought a civil lawsuit against pharmaceutical manufacturer GlaxoSmithKline, alleging that the company committed fraud by disseminating information about the off-label use of Paxil® (paroxetine) for treating depression in pediatric patients while, at the same time, withholding negative clinical data about the drug's effectiveness for that off-label indication.²¹⁰ In the settlement agreement, GlaxoSmithKline agreed to pay \$2.5 million in disgorgement and costs to the State of New York and agreed to publish summaries of all company-sponsored clinical trials since December 2000 (the date Glaxo Wellcome and

²⁰⁸ This dilution theory generally occurs when a drug manufacturer has effectively watered down its regulations-required warnings by causing either its sales representatives or its DTC advertisements to promote a wider use of the drug, to physicians or consumers, respectively. *See, e.g., Incollingo v. Ewing*, 282 A.2d 206, 222 (Pa. 1971) (holding that a drug manufacturer can be held to have breached his duty of reasonable care by promoting its product in such a manner as to nullify the printed label warnings); *accord Stevens v. Parke, Davis & Co.*, 507 P.2d 653, 661 (Cal. 1973).

²⁰⁹ *See James O'Reilly & Amy Dalal, Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 316 n.127 (2003) (citing *Buckman v. Plaintiff's Legal Committee*, 531 U.S. 341 (2001) and noting that "a direct claim of fraud upon the FDA would probably be rejected under the Supreme Court's approach in the comparable claim of medical device fraud")

²¹⁰ The Complaint also alleged that GlaxoSmithKline failed to properly disclose the mixed clinical trial results to physicians in medical information letters. Complaint at 10–11, 14–16, *New York v. GlaxoSmithKline, P.L.C.*, Civil Action No. 04-CV-5304 MGC (N.Y. Sup. Ct. June 2, 2004), available at <http://fl1.findlaw.com/news.findlaw.com/cnn/docs/glaxo/nyagglaxo60204cmp.pdf>.

SmithKlineBeecham merged).²¹¹ Under these hard-line terms, GlaxoSmithKline became the first major drug manufacturer to disclose publicly information on clinical drug trials. The case also demonstrated the effectiveness of pursuing off-label promotion under state fraud laws.²¹²

Federal fraud claims can be brought against a drug manufacturer for promoting off-label uses that result in the submission of false or fraudulent claims for reimbursement to the U.S. government, under the False Claims Act (FCA).²¹³ By its express terms, the FCA encompasses all types of fraud or misrepresentation that can result in financial loss to the federal government, which includes healthcare fraud.²¹⁴ The FCA has been interpreted by a minority of courts to require only the presentation of a false or fraudulent claim for payment or approval, without the additional element of a false record or statement.²¹⁵ Under such construction, even truthful, non-misleading statements made by drug manufacturers about the effectiveness of their drug products in off-label uses will constitute fraudulent representations under the FCA, if the government will not reimburse for those uses.²¹⁶ Increasingly, the FCA is being used for this very purpose, in *qui tam* or “whistleblower” actions (brought by an individual on behalf of the government), to police off-label promotion and to

²¹¹ Consent Order & Judgment at 6, *New York v. GlaxoSmithKline, P.L.C.*, Civil Action No. 04-CV-5304 MGC (N.Y. Sup. Ct. Aug. 26, 2004), available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04_attach1.pdf.

²¹² See Press Release, Office of the State of New York Attorney General Press Releases, *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.

²¹³ 31 U.S.C. § 3729(a)(1)–(2) (2005).

²¹⁴ See Ralph F. Hall & Robert J. Berlin, *When You Have a Hammer Everything Looks Like a Nail: Misapplication of the False Claims Act to Off-Label Promotion*, 61 *FOOD & DRUG L.J.* 653, 653–55 (2006).

²¹⁵ See, e.g., *United States ex rel. Franklin v. Parke-Davis*, No. 96-11651, 2003 U.S. Dist. LEXIS 15754, at *4 (D. Mass. Aug. 22, 2003) (citations omitted).

²¹⁶ *Id.* at *6 (holding that the only issue under § 3729(a)(1) is whether a false claim was presented to the government, and § 3729 does not require that the “cause” be fraudulent or otherwise independently unlawful). *But see* Hall & Berlin, *supra* note 214; *Edmonds v. Levine*, 417 F. Supp. 2d 1323 (D. Fla. 2006).

obtain large judgments or settlements from pharmaceutical manufacturers engaging in aggressive drug marketing strategies.²¹⁷

The most high-profile use of the FCA in recent years has been in the Neurontin® (gabapentin) litigation. Neurontin® was approved by the FDA in 1994 for use as a supplemental anti-seizure treatment in epilepsy patients and broadly marketed by the Parke-Davis division of Warner-Lambert, and then Pfizer.²¹⁸ Between 1995 and 2002, Neurontin®'s sales increased significantly and extended well beyond the relatively small epilepsy market to cover a variety of off-label populations, including patients suffering from pain disorders, migraines, bipolar disease, attention deficit disorder, restless leg syndrome and drug and alcohol withdrawal.²¹⁹

An investigation of Warner-Lambert's marketing practices began in 1996, when a former medical liaison for Warner-Lambert filed a *qui tam* suit under the FCA, claiming that the company had used fraudulent means to promote increased prescriptions of Neurontin® for off-label uses.²²⁰ The former employee alleged, and the U.S. Department of Justice (DOJ) later concluded, that the company's marketing efforts had included direct promotion of off-label uses to physicians and the Department of Veterans Affairs, financial underwriting of sham drug studies for off-label uses, offers of cash payments to physicians for reporting their prescribing practices, and various gifts and kickbacks to physicians

²¹⁷ The FCA provides for both treble damages (i.e., three times the amount of the false claim submitted to the government) and fines of between \$5,500 and \$11,000 per fraudulent claim. 31 U.S.C. § 3729(a) (2005); 28 C.F.R. § 85.3(a)(9) (1999). The *qui tam* plaintiff or whistleblower will receive 15–25% of the recovery, if the government joins the action, and 25–30% if the government does not. 31 U.S.C. § 3730(d)(1)–(2) (2005). According to the FCA Legal Center, FCA judgments and settlements against fraud-feasors in the last 11 years have totaled over \$12 billion. See Taxpayers Against Fraud Education Fund website: Top 20 Cases, <http://www.taf.org/top20.htm> (last visited Sept. 12, 2007).

²¹⁸ Warner-Lambert, including the Parke-Davis division, was acquired by Pfizer, Inc. in 2000. United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 44–45 (D. Mass. 2001).

²¹⁹ *Id.* at 45. See also Press Release, The U.S. Department of Justice Press Release, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.

²²⁰ *Franklin*, 147 F. Supp. 2d at 45–46.

for increasing their Neurontin® prescriptions for unapproved uses.²²¹ Ultimately, a global settlement was reached. Warner-Lambert agreed to pay the United States over \$430 million in penalties for its conduct.²²² Since the 2004 settlement, numerous other pharmaceutical manufacturers have made equally large payments to the government to settle FCA claims involving off-label marketing.²²³

Last, but certainly not least, is FDCA liability. Off-label promotion by drug manufacturers, in contrast to off-label prescription by physicians, is directly actionable under the FDCA. The FDCA provides for broad enforcement of off-label marketing violations through administrative, civil, injunctive and criminal actions, instituted by the FDA or the DOJ on behalf of the Department of Health and Human Services and the FDA. Penalties for off-label promotion under the FDCA are extensive and can include administrative seizure of drugs, injunctive relief against unlawful promotional activities, civil monetary penalties, disgorgement of profits, production step-downs, and related criminal penalties.²²⁴

Criminal liability can also attach under the FDCA for off-label promotion under the misbranding provisions, interpreted to provide “no adequate directions for [the off-label] use,” and then for manufacturing or otherwise placing that product into interstate

²²¹ *Id.* (noting that the case remained under seal for several years until 1999 when the DOJ announced the results of its investigations). Since then, many studies have assessed the impact of the such marketing practices on physicians. *See, e.g.,* Michael A. Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANN. INTERN. MED. 284, 284–93 (2006) (concluding that the pharmaceutical promotion of Neurontin® strongly influenced clinical decision-making by physicians).

²²² The former employee received a financial windfall of approximately \$24.64 million, as a portion of the civil recovery. *See* Press Release, U.S. Department of Justice, *supra* note 219.

²²³ As reported by the FCA Legal Center, the top 20 recoveries to date include a \$704 million settlement by Serono, \$435 million by Schering-Plough, \$266 million by AstraZeneca Pharmaceuticals, and \$257 million by Bayer Corp. These settlements resolved both civil liabilities and associated criminal charges relating to allegations of marketing fraud. *See* Taxpayers Against Fraud Education Fund website: Top 20 Cases, <http://www.taf.org/top20.htm> (last visited Sept. 12, 2007).

²²⁴ *See generally* 21 U.S.C. §§ 333–34 (2003).

commerce for such use.²²⁵ In the Warner-Lambert global settlement, Warner-Lambert agreed to plead guilty to two counts of criminal misconduct under the FDCA with regard to Neurontin® misbranding, for failing to provide adequate directions for use and for introducing into interstate commerce an unapproved new drug. For these violations Warner-Lambert paid over \$200 million in criminal fines.²²⁶

Over the past decade, the FDA and federal prosecutors have aggressively initiated misbranding actions against pharmaceutical and generic drug companies, pursuing both civil and criminal claims under the FDCA. Many consider such measures excessive. Historically, FDA enforcement began and ended with the public issuance of a Warning Letter or another punitive and precautionary statement to the drug manufacturer for promoting the off-label use. Few Warning Letters resulted in actual prosecution, as the public opprobrium surrounding each written reprimand was thought to serve as a sufficient penalty to fit the company's crime.²²⁷ Indeed, the use of these warnings by competitors in the market can create negative press that is more harmful and costly to a company than litigation itself.

More recently, however, the DOJ has taken an aggressive position on the criminal enforcement of off-label drug promotion by pursuing misbranding violations as federal crimes. The first criminal prosecution of a drug company for illegal promotion of a drug for unapproved uses was against Genentech in 1999, for its marketing practices surrounding the company's first product, Protropin® (somatrem for injection) growth hormone.²²⁸ This

²²⁵ The misbranding charge is derived from 21 U.S.C. §§ 331(a) and 352(f) (2004) ("adequate directions for use"). See also *supra* notes 131 and 132 and accompanying text.

²²⁶ See Press Release, U.S. Department of Justice, *supra* note 219.

²²⁷ All Warning Letters and Responses are available to the public and are posted online, at the FDA's Freedom of Information Reading Room website. See FDA's Electronic Freedom of Information Reading Room - Warning Letters and Responses, <http://www.fda.gov/foi/warning.htm> (last visited Sept. 12, 2007).

²²⁸ Protropin® growth hormone was the first therapeutic protein product to be manufactured and marketed by a biotechnology company. Genentech received FDA approval to market the drug in 1985. See Genentech: About Us, <http://www.gene.com/gene/about/corporate/history/timeline/index.jsp> (last visited Sept. 12, 2007).

landmark case resulted in a settlement of over \$50 million to settle the off-label promotion and marketing allegations (\$30 million in criminal fines and \$20 million in civil settlement).²²⁹ Since then, a surfeit of other lawsuits have been filed with conjoint criminal and civil claims under the FDCA.²³⁰

Further evidence of the ever-expanding scope of federal prosecution for off-label promotion occurred in April 2006. There, an individual physician consultant was arrested and charged with participating in the unlawful promotion of Xyrem® (gamma-hydroxybutyrate or GHB) for off-label uses on behalf of the drug's manufacturer, Jazz Pharmaceuticals, Inc.²³¹ The indictment charged that the doctor, both individually and as part of a conspiracy with the manufacturer, introduced a misbranded drug into interstate commerce and committed healthcare fraud.²³² In July 2007, a settlement was reached between the drug manufacturer and the United States Attorney's Office. The manufacturer agreed to pay \$20 million in penalties and victim compensation to resolve parallel criminal and civil investigations.²³³ The criminal misbranding charges that remain

²²⁹ In its plea agreement, Genentech admitted that it aggressively marketed Protropin® for uses other than the one approved by FDA. Protropin® had been approved for long-term treatment of children with growth hormone deficiency, but was being marketed and sold for the treatment of burns, childhood obesity and certain kidney disorders. *See* Plea Agreement, United States v. Genentech, Inc., Criminal No. 99-cr-0141-MJJ (N.D. Ca 1999), entered May 7, 1999.

²³⁰ For example, see the reported cases involving both criminal and civil settlements for FCA and FDCA claims, *supra* note 219.

²³¹ Press Release, The U.S. Att'ys Off., E. Dist. of N.Y., *Psychiatrist Charged With Conspiracy to Illegally Market the Prescription Medication Xyrem, Also Known as "GHB," For Unapproved Medical Uses on Behalf of Its Manufacturer* (Apr. 5, 2006), available at <http://www.usdoj.gov/usao/nye/pr/2006/2006apr05.html>. *See also, e.g.*, Alex Berenson, *Indictment of Doctor Tests Drug Marketing Rules*, N.Y. TIMES, July 22, 2006, available at <http://www.nytimes.com/2006/07/22/business/22drugdoc.html>.

²³² *See* Press Release, *Psychiatrist Charged With Conspiracy*, *supra* note 231. The relevant statutes are: 21 U.S.C. §§ 331(a), 333(a)(2) (2006) (misbranding); 18 U.S.C. §§ 1347, 1349 (2006) (healthcare fraud), and 18 U.S.C. § 2 (2006) (aiding and abetting).

²³³ The government's investigation began after a whistleblower suit was filed under the FCA by a former sales representative for Orphan Medical, a subsidiary of Jazz Pharmaceuticals, Inc. The civil settlement included payment to Medicaid participating states to resolve the FCA claims. The plea agreement included a guilty plea to one count of felony misbranding of a drug product for off-label uses under the FDCA. Press Release, The U. S. Att'ys Off., E. Dist. of N.Y., *Jazz Pharm., Inc. Agrees to Pay \$20*

pending against the individual physician are duly acknowledged to have “raised questions about free-speech issues and the government’s right to regulate the practice of medicine.”²³⁴

One final example of individual criminal liability arising under the FDCA is the DOJ’s targeted prosecution of pharmaceutical company corporate executives for off-label marketing. In May 2007, three senior executives of Purdue Frederick Company, Inc. and the company itself pled guilty to charges involving the criminal misbranding of OxyContin® (oxycodone), under the doctrine of vicarious liability as applied to the FDCA.²³⁵ The Attorney General’s Office advanced a rarely used theory that the executives were “responsible corporate officers” at the time the violations occurred and, thus, could be held strictly liable for failing to either prevent in the first instance or promptly correct the introduction of the misbranded drug into interstate commerce.²³⁶ Under the terms of the settlement, the company will pay over \$100 million in civil penalties, and the individuals will pay over \$34 million in disgorgement and criminal fines.²³⁷

By all accounts, this sedulous enforcement activity is expected to be just the tip of the iceberg. The DOJ is believed to have over

Million To Resolve Criminal and Civil Allegations In “Off-Label” Marketing Investigation (July 13, 2007), available at <http://www.usdoj.gov/usao/nye/pr/2007/2007jul13a.html>.

²³⁴ Alex Berenson, *Maker of Narcolepsy Drug Pleads Guilty in U.S. Case*, N.Y. TIMES, July 14, 2007, available at <http://www.nytimes.com/2007/07/14/business/14jazz.html>.

²³⁵ See Information, Attachment F to Plea Agreement, United States v. Purdue Frederick Co., Inc., Civil Docket No. 07-CR-29 JPJ, filed May 9, 2007, available at <http://www.vawd.uscourts.gov/PurdueFrederickCo/Main-Document.pdf>.

²³⁶ *Id.* at 3–4. See also Ropes & Gray Client Alert, *DOJ Intensifies Pressure Against Corporate Executives in Off-Label Marketing Arena* (May 24, 2007), available at http://www.ropesgray.com/files/Publication/713dad55-e014-43d7-85ac-1a589b15e542/Presentation/PublicationAttachment/840adccf-b1b0-4f8a-82db-1e30fe1e7112/Alert_May_24_2007_DOJ.pdf.

²³⁷ Civil Settlement Agreement, United States v. Purdue Frederick Co., Inc., Civil Docket No. 07-CR-29 JPJ; Plea Agreement as to Michael Friedman; Plea Agreement as to Howard R. Udell; Plea Agreement as to Paul D. Goldheim; all filed May 7, 2007, all documents available at <http://www.vawd.uscourts.gov/PurdueFrederickCo/default.asp>. In addition, the executives were sentenced to three years’ probation and 400 hours each of community service in drug treatment programs. See Barry Meier, *3 Executives Spared Prison in OxyContin Case*, N.Y. TIMES, July 21, 2007, available at www.nytimes.com/2007/07/21/business/21pharma.html.

150 investigations of pharmaceutical companies ongoing, involving 500 or more products.²³⁸ Pharmaceutical manufacturers would be well advised to operate under effective compliance programs if they wish to avoid the prosecutorial limelight. This is particularly true in view of the fact that, to date, the criminal prosecutions have made no clear distinction between the promotion of truthful information about the effectiveness of off-label indications and false or misleading claims for those uses. Judicial guidance on this point is scarce, because virtually all of the lawsuits have resulted in settlements and plea agreements. Companies are unwilling to take the risks associated with going to trial, including the risk of exclusion from participation in federal and state healthcare programs.²³⁹ For this reason, the true limits on the FDA's regulatory power to restrict off-label promotion has not been tested.

As was argued in criticism of the aggressive use of the FCA, any legal theory used to collect hundreds of millions of dollars in penalties and fines should be based upon a firm legal basis, or else it should trigger an extensive analysis of the law and the underlying policy by legislatures, courts, policy makers and academics.²⁴⁰ The final section of this Note reviews the currently ongoing analyses and debates surrounding FDA law and policy.

D. Proposals for FDA Reform

Determining what is prudent and practical public policy in the healthcare sphere is a constant challenge. Recently, the government has tipped the scales towards the end of tightly restricting drug promotion and the drug manufacturer's freedoms to inform the public about their products. However, this trend may not reflect an adequate balancing of innovator versus generic interests, as innovator pharmaceutical manufacturers are plainly

²³⁸ John R. Wilke, *Cases, Fines Soar in Fraud Probes*, WALL ST. J., June 7, 2005.

²³⁹ See generally 42 U.S.C. § 1320a-7 (2005). This section provides for both mandatory exclusion, upon conviction of a criminal offense relating to healthcare fraud or the "delivery of an item or service," and permissive exclusion, in which the government determines that certain forms of misconduct have occurred.

²⁴⁰ Hall & Berlin, *supra* note 214, at 674.

being more heavily targeted by the DOJ.²⁴¹ Accordingly, any proposed framework for improving FDA supervision and/or government enforcement in the context of the production and dissemination of information concerning off-label drug use must be evenhanded and effect a syncretic balance between the interests of innovators, generics, physicians and the public.

The next wave of FDA reform must also consider patent issues. Pharmaceutical lobbyists have long argued for better integration and consideration of the fairness of the FDCA and the corresponding FDA regulations in view of the patent laws and regulations. This monstrous task is quickly coming to a head with the emergence of follow-on biologics (FOBs), otherwise known as generic biologics or biosimilars. As patents and exclusivity rights are expiring on biotechnology drugs, i.e., drugs made by biological processes, a competitive but highly lucrative market in protein therapeutics is rapidly opening up for FOBs.²⁴² There is currently no FOB industry in the U.S. because there is no established way for the FDA to regulate the production and distribution of generic drugs made through living organisms.²⁴³ Legislators are, thus, wrestling with the difficult task of how to construct a regulatory mechanism that assures the safety and efficacy of FOBs that are

²⁴¹ Any endorsement of increased innovator liability, as a form of *noblesse oblige* for having gained a foothold in the blockbuster drug market, is outdated. A golden era for generic drugs is arriving, as many of the seminal patents on blockbuster medications are expiring. See, e.g., Stephanie Saul, *More Generics Slow Rise in Drug Prices*, N.Y. TIMES, Aug. 8, 2007, available at <http://www.nytimes.com/2007/08/08/business/08generic.html?ex=1344225600&en=e155928a7a102156&ei=5088&partner=rssnyt&emc=rss> (observing that over the next five years, patents will expire in brand name medications with more than \$60 billion in combined annual sales and bring forth a “tidal wave of generic drugs”).

²⁴² Biotech drugs are the fastest growing segment of the pharmaceutical market. Overall sales for therapeutic proteins are expected to top \$57 billion by 2010. Some of the largest biotech drugs soon to go off patent include: Genentech’s Nutropin® (patent expires in 2009); and Amgen’s drugs Procrit®, Neupogen® and Epogen® (all patents expire by 2013). Bruce S. Manhein, Jr. et al., *‘Follow-On Biologics’: Ensuring Continued Innovation in the Biotechnology Industry*, 25 HEALTH AFF. 394, 395 (2006).

²⁴³ Biotech drugs are produced by bacterial or mammalian cells that have been genetically engineered to produce the therapeutic protein. Traditional generics legislation deals only with generic drugs based on molecular compounds that can be produced synthetically. See *supra* Part I.

more difficult to produce than traditional generics and thus more difficult to substitute for the innovator drugs.²⁴⁴

Although the topic is well beyond the scope of this Note, in many ways, the issues confronting FOBs magnify those that exist for the unapproved uses of drugs.²⁴⁵ FOBs cannot be approved with the same ease or frequency as traditional generic drugs. Off-label indications are not being approved at the same frequency as a drug's first indication. The seeming inability to craft appropriate regulations for both sets of circumstances stems from the inherent difficulties associated with the trade-off between the costs of FDA approval and the desired access and availability of drugs in the marketplace. Ultimately, for FOBs, far more than for unapproved drug indications, a full complement of data will likely have to appear alongside the product to assure drug safety and efficacy.

Setting aside the issue of biologic drugs and FOBs, various other legislation has touted the benefits of data-heavy or evidence-based medicine, to minimize the uncertainty or guesswork involved in prescribing newly approved drugs.²⁴⁶ Proponents of these reformative measures recognize that unproven off-label prescribing practices can be harmful in some instances, for

²⁴⁴ *Id.*; See also Andrew Pollack, *In Biotech Brews, Questions of Consistency*, N.Y. TIMES, June 11, 2007, available at www.nytimes.com/2007/06/11/business/businessspecial3/11vat.html; Bernadette Tansey, *Are We Ready for Generic Biotech? Safety Concerns—and Enormous Profits—at Issue as Industry Braces for Copycat Drugs*, S.F. CHRON., July 15, 2007, available at <http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2007/07/15/BUGC2QVJIQ1.DTL>.

²⁴⁵ In fact, proposals were made to include the proposed biologics legislation in the same bill that addressed many issues surrounding drug safety and off-label uses of drugs. A combined FDA bill was approved by the Senate (*see discussion infra* text accompanying notes 248–251), but the merged bill was highly controversial, and ultimately it was decided that the biologics bill would need to be taken up separately. *See, e.g.*, Anna Wilde Matthews, *House Acts to Boost FDA Powers; Biotech Fight Looms*, WALL ST. J., July 12, 2007.

²⁴⁶ Evidence-based medicine aims for the ideal that medical practitioners should make conscientious, explicit, and sensible use of current best evidence in their everyday practice. It advocates the use of evidence in the decision-making aspects of medicine that depend on rational assessments of the risks and benefits of treatments. *See* Evidence-based Medicine, Wikipedia, http://en.wikipedia.org/wiki/Evidence-based_medicine (as of Sept. 12, 2007, 21:00 GMT); *see also* A.S. Elstein, *On the Origins and Development of Evidence-Based Medicine and Medical Decision Making*, 53 INFLAMM RES., SUPPL. 2:S184-9 (2004).

example, where an inefficient prescription could have been substituted for a more effective one. Numerous studies have indicated a need for more extensive post-marketing surveillance and risk assessment of approved drugs, to identify non-evidence-based prescribing practices and to distinguish those that are clinically reasonable from those that may be of concern.²⁴⁷

To this end, Congress undertook major legislative reform this year, to give the FDA increased financing to perform periodic reviews of approved drug usage and to require pharmaceutical companies to make data on active clinical trials publicly available and to perform post-approval studies.²⁴⁸ The Senate version of the legislation authorized a lengthy process for post-market FDA safety review of approved drugs and supplements, with improved analytical tools to assess potential safety problems.²⁴⁹ The legislation also sought to improve FDA surveillance of adverse effects throughout the life cycle of a drug product, in part by requiring better post-marketing diagnostics and systematic evaluations of off-label usage via its “risk evaluation and mitigation strategy.”²⁵⁰ The House version of the legislation added

²⁴⁷ A current problem with approved drugs is that post-market surveillance and late phase (i.e., phase 4) clinical trials are all too often either not conducted or else negative outcomes go unreported and are inaccessible to the public. See Radley, *supra* note 134, at 1025–26.

²⁴⁸ On May 9, 2007, the Senate passed S. 1082, “An Act to Amend the FDCA and the Public Health Service Act to Reauthorize Drug and Device User Fees and Ensure the Safety of Medical Products, and For Other Purposes,” sponsored by Sen. Edward M. Kennedy and also known as the FDA Revitalization Act or the Enhancing Drug Safety and Innovation Act of 2007. See also, e.g., Harris, *supra* note 177 (discussing the need for the legislative proposals to improve public safety monitoring of approved drugs whilst encouraging clinical innovation); Christopher Lee, *Senate Approves Bill on Drug Monitoring*, WASH. POST, May 10, 2007; Robert Pear, *Senate Approves Tighter Policing of Drug Makers*, N.Y. TIMES, May 10, 2007, available at <http://www.nytimes.com/2007/05/10/washington/10drug.html?partner=rssnyt&emc=rss>. The House of Representatives recently passed similar legislation, H.R. 2900, “The Food and Drug Administration Amendments Act of 2007,” on July 11, 2007. See Lisa Richwine, *Bill on Drug Safety, FDA Funding Clears House*, REUTERS, July 12, 2007.

²⁴⁹ See S. 1082, 110th Cong. § 102 (2007). The version as passed by the Senate removed provisions that limited the post-market safety activities to three years after approval of a new drug.

²⁵⁰ See S. 1082, § 201 (setting forth FDCA amendments to establish minimum standards to collect and assess post-marketing electronic health data in a post-market risk identification and analysis system). For a summary of the reform elements, see Mark

more severe penalties for violations of FDA safety laws, by authorizing increased civil monetary fines for repeated false or misleading DTC drug advertisements.²⁵¹

Another major purpose of the FDA reform legislation was to renew, from fiscal year 2008 through 2012, the program in which the drug industry pays user fees to the FDA.²⁵² The user fee system is intended to encourage drug makers to assess efficacy and safety issues earlier in drug development, to defray the administrative cost of reviewing new drug products and indications, and to assist in bringing new therapies to market more quickly.²⁵³ Overall, the Food and Drug Administration Amendments of 2007 (“FDAA”) represent the largest overhaul of FDA’s safety authority since 1962. The new law is sure to have both protective and pernicious effects—steps to enhance safety and monitoring of drug use will necessarily increase costs and restrict access to beneficial drugs. At its core, the FDAA gives the FDA increased power to act to ensure the continued safety of drugs post-approval and throughout the full life cycle of every drug product. New regulations or guidelines will undoubtedly be drafted to implement the FDA’s new authority.

McClellan, *Drug Safety Reform at the FDA—Pendulum Swing or Systematic Improvement?*, 356 NEW ENG. J. MED. 1700–02 (2007).

²⁵¹ Additional provisions permit the FDA to require pre-review of DTC advertisements. See Lisa Richwine, *Drug Safety Legislation Clears U.S. House Panel*, BOSTON GLOBE, June 21, 2007.

²⁵² Both H.R. 2900 and S. 1082 contained the proposed legislation, titled “Prescription Drug User Fee Amendments of 2007” (PDUFA IV), to renew the Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (renewed as part of the FDAMA and reauthorized in the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, 116 Stat. 594, FDCA §§ 735–736), which was set to expire in late September 2007. The House and Senate reached an agreement on omnibus FDA reform legislation just in time. The House passed H.R. 3580, the FDA Amendments Act of 2007, which includes PDUFA IV (but does not contain any provisions concerning FOBs), on September 19, 2007. The Senate also passed the reform legislation by unanimous consent on September 20, 2007. The legislation was signed into law by President Bush on September 27, 2007. Food and Drug Administration Amendments of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

²⁵³ See, e.g., The Associated Press, *Congress Moves to Increase Spending on Drug Safety*, INT’L HERALD TRIB., July 11, 2007.

CONCLUSION: THE BIG PICTURE

The rapid pace of discovery in the biotechnological and medical sciences over the last few decades has brought with it increased pressure on the FDA to expedite the approval process for potential new therapeutics.²⁵⁴ Recent legislative proposals on FOBs provide a prime example of immediate efforts to make medications available more quickly to the public. Yet, such efforts are coupled with scant measures to address the long-term safety implications of such changes. The FDA is in a constant state of playing catch up, as evidenced by the swift passage of the FDAA.²⁵⁵

Perhaps, the largest shift in the drug landscape over the last several decades has been the introduction of generic drug competition, both domestic and offshore, which has served to shift the regulatory balance away from drug safety and towards drug access and availability. From a market standpoint, the mere presence of generic drugs stifles the incentives of pharmaceutical companies to obtain further patent protection on and regulatory approval for new uses of approved drugs already on the market, because of a limited ability to recover against generic drug manufacturers for inducing patent infringement through crossover sales of generics for off-label uses.²⁵⁶

The medical community has also felt the effects of increased competition in the drug marketplace. Although an increase in drug availability can enrich patient care, at the same time, healthcare professionals are stymied in their ability to learn about off-label uses and to encourage further research and development on such uses. Most physicians simply do not have the time to conduct research on off-label uses and to assess contradictory findings. The healthcare imbroglio that ensues is reminiscent of the standard operating procedure in a James Bond film, where the professionals are given increasingly sophisticated and powerful professional gadgets, but are only able to use them under challenging and compromised conditions.

²⁵⁴ See Stepp, *supra* note 18, at 3.

²⁵⁵ Pub. L. No. 110-85, 121 Stat. 823 (2007).

²⁵⁶ See discussion *supra* notes 183–186 and accompanying text.

Efforts to quicken the pace at which drugs are approved and brought to market naturally shift the risk of liability for harm to later post-marketing stages of the drug lifecycle. The last few years have shown a direct relationship between attempts to accelerate drug approval and corresponding attempts to more stringently regulate drug promotion and marketing. The inherent tension between pre-market approval and post-market surveillance has a long history. A review of the past century of the FDA is instructive in that it provides a comprehensive framework for evaluating proposals for future change in the FDA's administrative authority and regulation of pharmaceutical drug approval and promotion. Efforts to improve the future should always reflect upon the past.

On one view, the FDA has come full circle in exerting its gatekeeper role in the healthcare industry by means of controlling drug labeling in the broadest sense. From its initial monitoring of fraudulent drug safety claims to its current surveillance of promotional labeling claims, the FDA has long endeavored to protect the public health through its restrictions on drug labels. It is perhaps not surprising that the FDA has been somewhat mired in its efforts to control an inherently uncontrollable market. Drug labeling restrictions are always post-hoc efforts to disclaim harm. Moreover, such constraints are likely to promote the exercise of behavior and practices that push the restrictive boundaries, simply to determine the *marge de manoeuvre* (i.e., wiggle room) within, as well as to see how far they can extend beyond.

These and other factors explain why the FDA's voluble attempts to regulate drug safety have been disparaged for failing to adequately address drug accessibility and vice versa. It is unfortunate that, in the politically charged public sector, squeaking hinges are the ones that get oiled and decisions are made that are not always balanced. The inherent unpredictability of the private sector economy further serves to emphasize the indomitable nature of healthcare and why much of the FDA's work consists of forming and reforming policy, in perpetual catch-up mode.

A safe and effective drug marketplace that both meets consumer needs and protects consumer interests is the great desideratum. FDA regulations will undoubtedly continue to shift

and sway to appease diverging public and private sector interests. Valuable reform efforts seek to achieve an acceptable level of regulatory oversight that balances the complex economic and policy objectives of meeting consumer demand for safe, efficacious and affordable healthcare with the ongoing needs of the medical community and the private sector innovators. The real function of the FDA is, and always will be, to best enable the medical professionals and pharmaceutical industries to provide treatment for disease, but to do no harm.

Notes & Observations