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OFF-LABEL DRUG PROMOTION IS LOST IN TRANSLATION: A PRESCRIPTION FOR A PUBLIC HEALTH APPROACH TO REGULATING THE PHARMACEUTICAL INDUSTRY'S RIGHT TO MARKET AND SELL ITS PRODUCTS

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INTRODUCTION

Constitutional adjudication regarding pharmaceutical manufacturers' First Amendment right to market and promote their products for off-label use is hardly a picture of clarity. Off-label use, the use of a drug or medical device for a condition for which the drug or device is not approved by the Food and Drug Administration (FDA),¹ is itself controversial, but whether pharmaceutical companies can promote such use creates unique tensions.² Under its jurisdictional authority, the FDA manages and monitors manufacturers' product marketing; to promote the FDA-approved use of a product consistent with its label, manufacturers commonly advertise, distribute various forms of promotional material in print, promote

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1. Off-label promotion practices has not been formally defined by statute but case law has provided some direction. The trial court in *Washington Legal Found. v. Kessler*, 880 F. Supp. 26, 28 n.1 (D.D.C. 1995), provided a workable definition to what off-label promotion may entail. According to the court, off-label promotion is triggered when a drug has been encouraged to be administered for a condition, dosage, and/or population that has not been tested and approved by the FDA. *Id.*

2. See, e.g., Joseph Leghorn et al., *The First Amendment and FDA Restrictions on Off-Label Uses: The Call for a New Approach*, 63 FOOD & DRUG L.J. 391 (2008) (discussing the need for a better approach in acknowledging new advancements in care and treatment of individual patients while still maintaining the safety of the public's health intact).

products during medical education seminars, and market uses of its products through their sales representatives.³ The FDA, however, does restrict manufacturers' ability to promote off-label uses of their products.⁴ On the one hand, FDA's restrictions on a pharmaceutical manufacturer's commercial practice of labeling and promoting its products for off-label use appear to serve a legitimate public health goal.⁵ On the other hand, these regulations arguably affect the pharmaceutical company's rights under the Free Speech Clause of the First Amendment.⁶ Despite this back-and-forth dynamic between the FDA's attempts to assure the safety and efficacy of therapeutic products and the pharmaceutical industry's concern that the agency's seemingly paternalistic measures are trampling on their First Amendment rights, at least one United States federal court has determined that the FDA's interest in safeguarding the public health outweighs a pharmaceutical sales representative's constitutional right to freedom of speech when that sales representative promotes several off-label uses of a drug to a physician.⁷ The decision in *United States v. Caronia*,⁸ coupled with the FDA's recent final guidance on the permissibility of disseminating information about off-label uses in printed format and at medical education programs,⁹ suggest that there is a legitimate focus by the FDA in regulating the promotion of off-label use.

Over the past decade, apprehension has escalated among government policymakers, patient advocates, and leaders in academic medicine about the influence of the drug and medical device industry on medical research, specialized medical education classes, and the industry practice of promoting off-label prescription use.¹⁰ The FDA at present imposes several restrictions on drug and

3. Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J. L. MED. & ETHICS 476, 477 (2009).

4. *Id.*

5. *Promotion of Unapproved Drugs and Medical Devices: Hearing Before the S. Comm. on Labor and Human Resources*, 104th Cong. (1996) (statement of William B. Shultz, Deputy Comm'r for Policy, Food & Drug Admin.).

6. Dresser & Frader, *supra* note 3, at 478.

7. *United States v. Caronia*, 576 F. Supp. 2d 385, 401–02 (E.D.N.Y. 2008).

8. *Id.*

9. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), available at <http://www.fda.gov/ohrms/dockets/98fr/fda-2008-d-0053-gdl.pdf> [hereinafter FDA GOOD REPRINT GUIDANCE] (discussing suggestions to the drug and medical device companies on appropriate off-label promotional practices).

10. See, e.g., ASS'N AM. MED. COLLS., INDUSTRY FUNDING OF MEDICAL EDUCATION: REPORT OF AN AAMC TASK FORCE 1–10 (2008), available at https://services.aamc.org/publications/showfile.cfm?file=version114.pdf&prd_id=232&prv_id=281&pdf_id=114 (noting the heavy presence of pharmaceutical industry influence within the medical education context via sponsored educational events, gifts, distribution of prescription drug samples directly to health care practitioners, and other benefits); Niteesh K. Choudhry et al., *Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry*, 287 JAMA 612 (2002) (conducting a study clinicians and their

device manufacturers from promoting unapproved uses of drugs and devices, even though the promotional information may very well be factually supported.¹¹ Although under the Food, Drug and Cosmetic Act (FDCA),¹² the current federal policy authorizes drug manufacturers to market and label drugs only for uses that have received approval from the FDA,¹³ physicians are free to issue off-label prescriptions to a patient for treatment of a medical condition for which the drug has not undergone standardized safety and efficacy testing.¹⁴ However, not only have courts recurrently held that numerous off-label drug uses can be appropriate modes of therapy,¹⁵ FDA has frequently recognized that under certain medical circumstances, some off-label drug uses are an appropriate way to medically treat a patient.¹⁶ This alarmingly regular practice of doctors prescribing off-label uses of drugs has given rise to drug companies advertising to doctors in order to encourage prescriptions for off-label uses of drugs, even after some companies have incurred criminal and civil liabilities for doing so.¹⁷ Unlike the medicines prescribed for FDA-approved treatments, an argument can be made that the practice of promoting off-label use adversely affects the public's health because no safeguards are in place to protect the patient from unsafe or ineffective medical care. Regulatory oversight rather than self-regulation by drug companies should set the standard in off-label drug promotion to physicians. A modification of the current approaches to off-label promotion is immediately needed.

While the pharmaceutical industry claims that promotion of off-label use is, at its core, commercial speech in the food and drug law context and thus entitled to

possible influence by their colleagues' relationships with pharmaceutical companies); Catherine D. DeAngelis & Phil B. Fontanarosa, *Impugning the Integrity of Medical Science: The Adverse Effects of Industry Influence*, 299 JAMA 1833 (2008) (discussing instances of pharmaceutical and medical device companies' profound influence on the medical profession and to their scientific research studies and publications); Robert Steinbrook, *Financial Support of Continuing Medical Education*, 299 JAMA 1060 (2008) (critiquing medical education and its dependence on financial support from pharmaceutical and medical device companies).

11. Richard C. Ausness, "There's Danger Here, Cherie!" *Liability for the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, 73 BROOK. L. REV. 1253, 1259-62 (2008).

12. FDA's ability to prohibit such dissemination of drug use information traces back to when Congress empowered FDA, by the passage of the Food, Drug and Cosmetic Act (FDCA), to regulate prescription drug labels. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-399 (2006)). At the time the FDCA was enacted in 1938, it established the requirements of drugs needing adequate labeling to promote and assure safe usage by the public. *Id.*

13. James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76 (1998).

14. *Id.* at 76, 78-79.

15. See, e.g., *Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996); *Ortho Pharm. Corp. v. Cosprophar, Inc.*, 32 F.3d 690, 692 (2d Cir. 1994); *Upjohn Co. v. MacMurdo*, 562 So. 2d 680, 683 (Fla. 1990)

16. Beck & Azari, *supra* note 13, at 79.

17. See *infra* Part I.B.

First Amendment protection afforded to commercial speech in general,¹⁸ this constitutional protection is not an absolute right uniformly granted to commercial entities.¹⁹ Although off-label promotion may violate the FDCA, there is currently no consensus on the extent to which the FDA can regulate commercial promotional truthful messages between a pharmaceutical manufacturer and a licensed doctor.²⁰ Because no definitive line of law or regulation has been established within this realm of government restriction and commercial promotion and because off-label prescribing by doctors is a widely accepted practice, sometimes even constituting the standard of care in particular circumstances,²¹ the pharmaceutical industry has continued to aggressively assert its First Amendment rights to promote its products in an attempt to lessen regulatory interference by FDA.²²

How much, then, is the social cost of meeting FDA safety and effectiveness standards prior to promotion of off-label uses of approved drugs, or prior to dissemination of physician-reviewed journal articles for off-label uses? Just how much regulatory oversight to administer to off-label promotion, however, is a question over which proponents of regulatory review of off-label promotion and the pharmaceutical industry sharply disagree.²³ The direction in which off-label promotion has been heading should not be ignored.²⁴ Whether the pharmaceutical companies are promoting products in a truthful manner or distributing reprints of peer-reviewed medical journal articles that are scientifically sound has been recently shown to be suspect.²⁵ While off-label marketing efforts are commercial in

18. See Comments of Pfizer, Inc., FDA Dkt. No. 02N-0209, at 8–9, 11–12, 165 (Sept. 13, 2002), available at <http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091602/80027f2d.pdf>.

19. See 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 (1999) (examining the comprehensive history of the changing definitions of commercial speech since the origination of the commercial speech doctrine in the context of off-label research dissemination).

20. Mark Ratner & Trisha Gura, *Off-Label or Off-Limits?*, 26 NATURE BIOTECHNOLOGY 867, 873–74 (2008).

21. Emily A. Largent et al., *Going Off-Label Without Venturing Off-Course*, 169 ARCHIVES OF INTERNAL MED. 1745, 1745 (2009).

22. See, e.g., Gina Shaw, *Is Off-Label Marketing a First Amendment Right? Allergen Asks in a Lawsuit Against FDA Over Botulinum Promotion*, 9 NEUROLOGY TODAY 20 (2009) (discussing Allergen's, the manufacturer of Botulinum toxin type A (Botox) recent lawsuit claiming that the current prohibition of off-label promotion violate its First Amendment right to share relevant information to physicians on a new use of a drug).

23. Ratner & Gura, *supra* note 20, at 874–75.

24. See Troyen A. Brennan et al., *Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 JAMA 429 (2006). According to one study, an estimated ninety percent of the \$21 billion marketing budget of the pharmaceutical industry has reportedly been directed at physicians. *Id.* at 430.

25. Bruce M. Psaty & Wayne Ray, *FDA Guidance on Off-Label Promotion and the State of the Literature from Sponsors*, 299 JAMA 1949, 1950 (2008). In leading up to these promotional efforts, large amount of funds by the pharmaceutical industry have been shown to have been shuffled toward marketing initiatives. In 2002, for example, the ten largest U.S. drug manufacturers spent thirty-one

nature, they are nonetheless inextricably linked to patients consuming therapeutic products that have not undergone efficacy studies.²⁶

Evaluating questions relating to the government's prohibition against off-label promotion in conjunction with freedom of commercial expression and what is deemed as protected speech or a permissible form of regulatory policy requires contextual analysis, especially in light of the recent ruling in *Caronia* and the FDA's latest guidance on promotional materials used or distributed by pharmaceutical manufacturers. This Comment seeks to emphasize the perspective of the *Caronia* court's ruling and the impact it can provide on the current pharmaceutical industry's practice of promoting their products to physicians for off-label use. In the United States, off-label drug use is pervasive and given that both its risks and benefits are comprehensively recognized by the medical community,²⁷ the need to contextualize this as a public health dilemma is ripe. In addressing the unremitting tension that exists between government regulation and private sector commercialism with respect to off-label promotion, this Comment will argue for a more balanced oversight of the pharmaceutical industry in three parts.

Part I examines the existence of a public health initiative within the context of off-label advertising.²⁸ It evaluates the FDA's off-label use policy and its regulatory approaches on the promotion of off-label uses by pharmaceutical manufacturers. In Parts II and III, this Comment will turn to two recent developments: (1) the holding of the Eastern District of New York in *Caronia*,²⁹ and (2) the FDA's recent guidance directed at the pharmaceutical industry's practice of distributing medical journal articles and other scientific publications to physicians on unapproved new uses of drugs.³⁰ This Comment will conclude by underscoring the need to attain a balance between consumer protection and the pharmaceutical industry's constitutionally protected freedom to communicate about innovative features of its products.³¹ Certainly this policy constricts the industry's right to freely engage in a

percent of revenues on marketing but only fourteen percent on research and development of their products. Marcia Angell, *Excess in the Pharmaceutical Industry*, 171 CANADIAN MED. ASS'N J. 1451, 1452 (2004).

26. David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES OF INTERNAL MED. 1021 (2006). A recent study concluded that seventy-three percent of all off-label uses fail to show sufficient evidence of efficacy, and that ninety-six percent of the most prevalent off-label uses for psychiatric treatment lack efficacy findings. *Id.* at 1023.

27. Daniel B. Klein & Alexander Tabarrok, *Who Certifies Off-Label?*, 27 REGULATION 60, 60–61 (2004).

28. *See infra* Part I.

29. The court held that the FDA's interest in protecting the public health outweighed a pharmaceutical sales representative's constitutionally protected right to freedom of speech despite the fact that the practice of utilizing off-label use by physicians is not itself illegal. *United States v. Caronia*, 576 F. Supp. 2d 385, 401–02 (E.D.N.Y. 2008).

30. *See infra* Part II.

31. *See infra* Part III.

commercial market, but the engagement can proceed in a calculated, responsible manner to better ensure the overall welfare of the patient population.

I. WHAT IS A PUBLIC HEALTH PROBLEM AND IS IT APPLICABLE TO OFF-LABEL PRESCRIBING?

A. Public Health—Then and Now

The scope and nature of public health as a field has evolved into a broadly and deeply encompassing discipline. The practice of public health emerged at the turn of the twentieth century when state health departments began to regulate communicable disease outbreaks, unsanitary or unsafe conditions in a community,³² and occurrences of vaccine-preventable diseases,³³ with the aim of improving and ensuring the public's health. But as community health boundaries were established, new public health problems emerged and an urgent need to respond became warranted by justifiable and appropriate government interventions, oftentimes at the expense of individual liberties and interests, for the overall benefit of the public health.³⁴ Although the focus of public health measures initially began with response to infectious diseases, unfolding public health threats led to an expansion in numerous regulatory measures directed towards improvement of the public health:³⁵ legislative directives to minimize food-borne diseases,³⁶ government decrees to prevent and control chronic disease,³⁷ policy enactments to prevent and curb tobacco use³⁸ and governmental management in correcting and controlling environmental health risks,³⁹ to name a few.

With this as the backdrop to the development of public health activities and its inextricable connection to law, the work and governmental efforts to organize in order to minimize causes of illness to the health of a population paved the path

32. JAMES A. TOBEY, *PUBLIC HEALTH LAW: A MANUAL OF LAW FOR SANITARIANS* 10–13 (1926).

33. James Colgrove & Ronald Beyer, *Manifold Restraints: Liberty, Public Health, and the Legacy of Jacobson v. Massachusetts*, 95 AM. J. PUB. HEALTH 571, 572 (2005).

34. See LAWRENCE O. GOSTIN, *PUBLIC HEALTH LAW: POWER, DUTY, RESTRAINT* Part II (2d ed. 2008).

35. INST. OF MED., *THE FUTURE OF PUBLIC HEALTH* (1988), reprinted in *PUBLIC HEALTH LAW AND ETHICS: A READER* 37, 38 (Lawrence O. Gostin ed., 2002) [hereinafter IOM REPORT]; see also INST. OF MED., *THE FUTURE OF THE PUBLIC'S HEALTH IN THE 21ST CENTURY* (2003) (an updated report detailing the current public health infrastructure and its evolving relationships with governmental public health agencies, policymakers, the general population, and the health care delivery system).

36. Leslie Kux et al., *Control of Foodborne Diseases*, in *LAW IN PUBLIC HEALTH PRACTICE* 361–84 (Richard A. Goodman et al. eds., 2007).

37. Angela K. McGowan et al., *Prevention and Control of Chronic Disease*, in *LAW IN PUBLIC HEALTH PRACTICE*, *supra* note 36, at 402–26.

38. Richard A. Daynard et al., *Prevention and Control of Diseases Associated with Tobacco Use Through Law and Policy*, in *LAW IN PUBLIC HEALTH PRACTICE*, *supra* note 36, at 427–51.

39. Daniel D. Stier et al., *Environmental Health and Protection*, in *LAW IN PUBLIC HEALTH PRACTICE*, *supra* note 36, at 478–505.

toward a widening definition of public health. Lawrence O. Gostin provides an excellent definition of public health law and the complexities inherent within the ever-developing scope of public health:

Public health law is the study of the legal powers and duties of the state, in collaboration with its partners (e.g., health care, business, the community, the media, and academe), to ensure the conditions for people to be healthy (to identify, prevent, and ameliorate risks to health in the population), and of the limitations on the power of the state to constrain for the common good the autonomy, privacy, liberty, proprietary, and other legally protected interests of individuals. The prime objective of public health law is to pursue the highest possible level of physical and mental health in the population, consistent with the values of social justice.⁴⁰

This definition directs awareness to the many circumstances that influence health and wellness, underlining the vast dimensions of public health and legitimizes its interest in not only economic, social, and political aspects but also medical care factors that affect health and illness. The definition's premise, one that other proponents of public health have also adopted,⁴¹ that society has an interest in the health of its members indicates that assuring and improving health conditions is, in essence, acting collectively for the public's own self-interest. Therefore, the claim that improving, assuring, and protecting the well-being of others affords benefits to all has developed into a core tenet of public health.⁴²

Just as public health legislation and measures have taken the form of mandatory reporting of infectious diseases, immunization requirements for children prior to entry of school, fluoridating of community water systems, and requirements for safety and efficacy in foods and drugs, off-label promotion practices can be placed within the gamut of public health regulated activities. With the growth of industrialized commerce and urban communities who need rapid manufacturing of drugs for medical treatments, governmental intervention is needed to provide basic safety protection and efficacy standards in consumer consumption of these chemically potent medical products. Government has an established authority for exercising oversight over retail food companies, sewage

40. GOSTIN, *supra* note 34, at 4.

41. Charles-Edward A. Winslow, *The Untilled Field of Public Health*, 2 MOD. MED. 183 (1920); see generally Jean C. O'Conner et al., *CONCURRENT SESSIONS: Closing Remarks: Conference Synopsis and Observations*, 30 J. L. MED. & ETHICS 210, 214 (2002) (providing a summary of the current status of public health and its inextricable connection to a broad range of health-laws).

42. In 1988, the Institute of Medicine defined the public health's objective as working towards "fulfilling society's interest in assuring conditions in which people can be healthy." IOM REPORT, *supra* note 35, at 38.

and water systems, occupational health and safety conditions, consumer product safety issues, and drug manufacture safety and efficacy.⁴³

Critics of the expansive scope of public health have claimed that government regulation in the name of public health overreaches by delving into areas that are inherently political and commercial, and in addition, that government lacks the expertise and training to sufficiently keep up-to-date with diverse public health initiatives.⁴⁴ Policies based on such an argument are misconceived within the context of off-label promotion; without an appropriate check on the promotional efforts that encourage off-label use, questionable exchanges between drug companies and physicians will persist at the expense of the public's health.⁴⁵ Notwithstanding off-label prescribing as legal and recurrent in some medical situations, the practice itself is dangerous because it is often issued to patients without the off-label use having undergone any comprehensive evaluation of data showing evidence of either its benefits or risks for the attempted treatment of a medical problem.⁴⁶ The present challenge for ensuring the health and quality of life of Americans who use medication off-label is clear. A collaborative system is needed to influence drug efficacy standards and transparency so as to ultimately promote delivery of the best therapeutic benefit to the public and not encourage risky and ineffective medical treatments.⁴⁷

43. BERNARD J. TURNOCK, *PUBLIC HEALTH: WHAT IT IS AND HOW IT WORKS* 18–19 (4th ed. 2009).

44. Compare Richard A. Epstein, *Let the Shoemaker Stick to His Last: A Defense of the "Old" Public Health*, 46 *PERSPECTIVES IN BIOLOGY & MED.* S138 (2003) (arguing that the modern view of what encompasses a public health issue ought to be narrowly applied rather than broadly utilized), with Lawrence O. Gostin & M. Gregg Bloche, *The Politics of Public Health: A Response to Epstein*, 46 *PERSPECTIVES IN BIOLOGY & MED.* S160 (2003) (critiquing the claim that modern public health overreaches in its application to "new" social circumstances).

45. See Eric G. Campbell, *Doctors and Drug Companies—Scrutinizing Influential Relationships*, 357 *NEW ENG. J. MED.* 1796, 1796 (2007) (noting various instances where physician-industry relationships can have negative consequences within the health care system); Robert M. Sade, *Dangerous Liaisons? Industry Relations with Health Professionals*, 37 *J. L. MED. & ETHICS* 398, 399 (2009) (reporting that sponsored continuing medical education programs by drug companies can be "associated with increased prescribing of the particular companies' products").

46. Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 *NEW ENG. J. MED.* 1427, 1427 (2008). An assertion of off-label use signifies that FDA scientists have not yet approved an efficacy claim of a drug by the scientific standards promulgated by the "New Drug Application" filing requirements. *Id.* For a description of what an FDA-approved drug application requires and when it can refuse or withdraw an approved application, see 21 U.S.C. § 355(b), (d)–(e) (2006) (providing a non-exclusive list of reasons for FDA to reject a drug approval application); *Edison Pharm. Co. v. FDA*, 600 F. 2d 831, 837 (D.C. Cir. 1979) (explaining the value and need for a showing of "substantial evidence" that a drug is objectively effective for its intended medical use).

47. Dresser & Frader, *supra* note 3, at 483–84.

B. FDA's Regulatory Authority in the Context of Off-Label Promotion

Pharmaceutical regulation in the United States over off-label promotion practices⁴⁸ between the industry and physicians is of topical debate. Since enactment of the FDCA in 1938, the FDA has had the authority to monitor and scrutinize the promotional materials of pharmaceutical companies, including print and Internet advertisements, broadcast announcements, and materials produced for dissemination to health care practitioners and patients, and used by pharmaceutical sales representatives.⁴⁹ The purpose of FDA oversight is to establish a process for ensuring that promotional materials are being communicated in a manner that is truthful in its representation of a product, not misleading, and substantiated by evidence from clinical trials or clinical experience.⁵⁰ The FDA implements their regulatory authority by reviewing various forms of promotional materials, issuing warning letters⁵¹ and injunctions against pharmaceutical manufacturers, and in some circumstances, forwarding cases of off-label promotion for criminal investigation.⁵²

Although the FDCA does not explicitly prohibit the promotion of off-label uses, two federal provisions effectively provide the FDA with authority to oversee manufacturers' product marketing.⁵³ By utilizing the FDCA's labeling and misbranding provisions, the FDA uses its regulatory power to limit a manufacturers' freedom to advertise products for off-label uses.⁵⁴ Notwithstanding FDCA's regulatory constraints on off-label promotion, pharmaceutical companies are allowed to reply to unsolicited inquiries from health care practitioners and other persons in general about unapproved uses.⁵⁵ While on the one hand, doctors are permitted to prescribe an FDA-approved drug for *any* use,⁵⁶ they generally do not

48. *Id.*

49. T. Abrams, *The Regulation of Prescription Drug Promotion*, in *ETHICS AND THE PHARMACEUTICAL INDUSTRY* 153, 154 (M.A. Santoro & T.M. Gorrie eds., 2005).

50. Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 *NEW ENG. J. MED.* 1557, 1558 (2009).

51. See, e.g., Press Release, Food & Drug Admin., FDA Orders 2 Companies to Stop Marketing Unapproved Nitroglycerin Tablets (Mar. 16, 2010), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm204744.htm> (noting that FDA has issued two warning letters to Glenmark Generics and Konek Inc. instructing them to stop promoting Nitroglycerin tablets for off-label uses). For a discussion of emerging issues in FDA regulation, see Jeffrey M. Senger, *Emerging Issues in FDA Regulation: Warning Letters, Internet Promotion, and Tobacco*, 13 *J. HEALTH CARE L. & POL'Y* 211 (2010).

52. Abrams, *supra* note 49, at 154.

53. S.D. Danzis, *Off-Label Communications and Prescription Drugs*, in *ETHICS AND THE PHARMACEUTICAL INDUSTRY*, *supra* note 49, at 184, 188.

54. Dresser & Frader, *supra* note 3, at 477.

55. Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 *Fed. Reg.* 59,820, 59,823 (1994).

56. Largent et al., *supra* note 21, at 1745.

disclose to patients that the drugs they are prescribing have sometimes been marketed to them by pharmaceutical salespeople,⁵⁷ and even by doctors employed by pharmaceutical companies to promote off-label uses to other doctors,⁵⁸ for uses that have not met safety and efficacy requirements set forth by the FDA. This tension between health care practitioners, the pharmaceutical industry, and FDA's authority in regulating the marketing of and the dissemination of off-label information has created some difficulty in monitoring off-label promotion in a standardized way, leaving off-label promotional products and activities today largely disorganized and unchecked.⁵⁹

1. FDA's Prohibition Against Off-Label Promotion: Labels and Misbranding

FDA uses two provisions to oversee manufacturer's product marketing efforts. First, the FDCA makes it unlawful for a manufacturer to introduce a drug into interstate commerce with the intent that it be marketed for an off-label function,⁶⁰ permitting a drug to enter interstate commerce only when the drug and its label has received FDA approval.⁶¹ FDA regulation states that "a new drug may not be approved for marketing unless it has been shown to be safe and effective for its intended use(s)."⁶² Because FDA approval is contingent upon a product's intended use(s), the required labeling that accompanies the product must precisely reflect its approved use(s).⁶³ As a result, if the manufacturer of the drug is found to have included information about off-label uses in its labeling information, thus failing to provide what the FDA deems as "adequate directions for its approved

57. *Doctors Should Disclose Off-Label Prescribing to Their Patients, Experts Argue*, SCI. DAILY, Nov. 11, 2008, available at <http://www.sciencedaily.com/releases/2008/11/081110223328.htm>.

58. See, e.g., David Evans, *Big Pharma's Crime Spree*, BLOOMBERG MARKETS, Dec. 2009, at 76–78 (reporting that when Dr. David Franklin worked as a medical liaison for Warner-Lambert Co. before Pfizer Inc. had purchased the company in 2000, which was previously owned by Parke-Davis, Inc., his manager encouraged him, along with other doctors, to utilize his doctorate as a badge in order to induce physicians to prescribe Neurontin for off-label use, to children in some cases, even if it meant withholding reported harmful side-effects to the physicians, thus undermining patients' general welfare).

59. GOV'T ACCOUNTABILITY OFF., PUB. NO. GAO-08-835, *PRESCRIPTION DRUGS: FDA'S OVERSIGHT OF THE PROMOTION OF DRUGS FOR OFF-LABEL USES* 5, 31 (2008).

60. 21 C.F.R. § 202.1(6) (2009).

61. 21 U.S.C. § 355(a) (2006).

62. 21 C.F.R. § 310.303(a). The FDCA explicitly states that new pharmaceutical drugs cannot be distributed in interstate commerce unless the proprietor of the drug illustrates to the FDA that the drug is safe and effective for each of its intended medical uses. 21 U.S.C. § 355(a), (d).

63. A drug's package, along with any inserts, constitutes "labeling." 21 U.S.C. § 321(k), (m). The FDA has also considered various forms of promotional printed materials related to a drug to fall under "labeling." 21 C.F.R. § 202.1; see also *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 55 (D.D.C. 1998) (finding that not only are package inserts that accompany a drug "labels" but also "nearly every form of drug company promotional activity, including booklets, pamphlets, mailing pieces, bulletins, and all literature that supplements, explains, or is otherwise textually related to the product" amounts to labeling); *United States v. Vitamin Indus., Inc.*, 130 F. Supp. 755, 765–66 (D. Neb. 1955) (posters on display that contained a description about a use of a drug shipped separately from the drug were found to fall under FDA's "labeling" regulations).

use(s),”⁶⁴ the manufacturer will have violated the FDCA, ensuing then in the mislabeling of the drug’s original FDA-approved label. The second provision bans manufacturers from introducing into interstate commerce a “misbranded” drug.⁶⁵ A drug is deemed to be misbranded if its label contains misleading information, incorporates information about unapproved uses, or fails to include information that supplements the safe use of the FDA-approved applications.⁶⁶ In addition to these two federal provisions, FDA also has the authority to seize misbranded drugs that have been introduced into interstate commerce⁶⁷ enjoin companies who unlawfully promote drugs,⁶⁸ and in some instances, it also has the capacity to seek criminal penalties for off-label marketing.⁶⁹

2. *An Expansion to FDA’s Scope of Off-Label Restrictions: The Food & Drug Administration Modernization Act*

In the mid-1990’s, major effort by lobbyists for the pharmaceutical industry sought to soften FDA’s restrictions against off-label promotion.⁷⁰ In 1997, several amendments to the FDCA were passed by Congress granting authority to the FDA to regulate the distribution of information by pharmaceutical manufacturers to health care providers concerning FDA-approved and off-label uses.⁷¹ Codified in section 401 of the Food & Drug Administration Modernization Act (FDAMA), manufacturers were permitted to disseminate information in relation to an off-label use, as long as the manufacturer abided by specified requirements:

- (1) Submission of a new drug application for the proposed new use;

64. See FDA Guidance Document: Decision in *Washington Legal Found. v. Hanney*, 65 Fed. Reg. 14,286, 14,286 (Mar. 16, 2000); but see Mark E. Boulding, *The Statutory Basis for FDA Regulation of Scientific and Educational Information*, 4 J. PHARM. & L. 123, 138–39 (1995) (arguing that the FDA’s definition of “intended use” is too comprehensive).

65. 21 U.S.C. § 331. For an illustration of how the FDCA’s misbranding doctrine operates, see *Nature Food Centres, Inc. v. United States*, 310 F.2d 67 (1st Cir. 1962). *Nature Food Centres, Inc.* was found to have misbranded Hemo-Glo. The company had promoted its FDA approved use for a “dietary supplement,” but it had also promoted the drug as having the ability to restore gray hair to its natural color. *Id.* at 70. Because the drug’s label only consisted of the FDA-approved dietary supplement use, the court sided with the government and held that *Nature Food Centres, Inc.* misbranded Hemo-Glo due to its failure to abide by FDA’s labeling requirements. *Id.* at 71.

66. 21 U.S.C. § 331(k). Any visual material that is distributed by a manufacturer that explains the uses of a drug can be considered as part of the drug’s labeling, even if the article of information is not included within the drug’s packaging. See, e.g., *Kordel v. United States*, 335 U.S. 345, 347–48 (1948) (finding a separate literature publication pertaining to a drug’s suggested usage as constituting a supplement to the label of the product’s packaging).

67. 21 U.S.C. § 334(a).

68. *Id.* § 332(a).

69. *Id.* § 333.

70. James O’Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANN. HEALTH L. 295, 297 (2003).

71. Food & Drug Admin. Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified as amended at 21 U.S.C. § 301–399).

- (2) Distribution of information must not be abridged, false, misleading, or posing significant health risks to the public;
- (3) All clinical research cited to in the disseminated materials must be the work of the manufacturer;
- (4) Mandatory submission to the FDA of a copy of the materials to be distributed sixty days prior to dissemination; and
- (5) Complete disclosure in all disseminated materials to recipients that the materials pertain to an unapproved use of the drug.⁷²

FDAMA also required drug manufacturers to keep records, and to report to FDA as needed, regarding an off-label's medical impact subsequent to the dissemination of material of an unapproved use. If the manufacturer failed to comply with these requirements, the FDA could then have issued an order terminating the distribution of informational materials until sufficient corrective action was taken.⁷³

Under FDAMA's section 401, manufacturers were given the opportunity to advertise off-label uses of their products as long as they adhered to the requisite conditions prior to disseminating off-label informational materials to healthcare practitioners.⁷⁴ By adhering to these requirements, section 401 provided pharmaceutical companies a safe harbor protection from FDCA misbranding violations.⁷⁵ However, if an allegation was made that a manufacturer had engaged

72. *Id.*

73. *FDA Proposes Rules for Dissemination Information of Off-Label Uses*, HHS NEWS, June 5, 1998, available at <http://www.scienceblog.com/community/older/archives/M/2/fda1150.htm>.

74. This 1997 amendment to the FDCA, mandating manufacturers to abide by several requirements when distributing promotional materials on off-label uses, prompted litigation relating to manufacturers' promotional statements about their products as qualifying as commercial speech, and thus, protected from mandatory constraints under the First Amendment. In the late 1990s, a federal court held that the provisions in section 401 of FDAMA were more restrictive than necessary to advance FDA's interest in establishing grounds for manufacturers to obtain FDA approval for off-label uses. *Washington Legal Found. v. Henney*, 56 F. Supp. 2d 81, 86–89 (D.D.C. 1999); *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72–74 (D.D.C. 1998). The court reasoned that some of the mandatory provisions on promotion unnecessarily curtailed manufacturers' constitutionally protected commercial speech rights. *Henney*, 56 F. Supp. 2d at 86–89. The court then ruled that FDA could mandate manufacturers to disclose their financial interests and that the promoted use has not yet been approved by the FDA, however, FDA could not require manufacturers to submit for approval the promoted off-label uses or require submittal to the FDA of the materials on off-label uses for review. *Id.* at 87, 89. The government appealed this ruling, but during the appellate argument, the contested section 401 provisions were described as simply a "safe harbor" for manufacturers' conduct rather than regulatory requirements, and subsequently, the case was dismissed. *Washington Legal Found. v. Henney*, 202 F.3d 331, 335 (D.C. Cir. 2000).

75. Richard Cooper, *The WLF Case Thus Far: Not with a Bang, But a Whimper*, 55 FOOD & DRUG L.J. 477, 480–84 (2000) (discussing *Washington Legal Found. v. Friedman*'s appeal and its subsequent holding in relation to FDAMA's enforcement provisions against a manufacturer's dissemination of information about off-label uses of their products). Under FDA's interpretation of the safe harbor provision, if a manufacturer fulfilled FDAMA's section 401 statutory requirements, the FDA would deem the off-label promotional practices to be in compliance with government oversight, and thus, the drug or medical device manufacturer would be protected from prosecution. FDA Guidance Document: Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14,286, 14,287 (Mar. 16, 2000).

in off-label promotional practices and the safe harbor provisions were not met, then a violation of the statute would have occurred,⁷⁶ leaving FDA free to exercise misbranding charges against the manufacturer.⁷⁷ The passage of section 401 of FDAMA serves as an illustration of the efforts FDA made to compel all incoming claims of drug effectiveness to undergo assessments by clinical data results and regulatory review prior to the promotion, whether oral or written, being made to prescribing physicians. Members of the American Medical Association have remarked that section 401 was a “meticulously crafted, bipartisan provision [that established] both a suitable mechanism and pertinent safeguards that assure[d] the information manufacturers disseminate[d was] both appropriate and credible.”⁷⁸ Although section 401 functioned as a voluntary government provision, it provided a compromise to the pharmaceutical industry to engage in off-label promotional efforts but in a fixed manner that not only established safety and efficacy standards for new uses of FDA approved products but also hastened the development and accessibility of new medical treatments, for the benefit of the public health.⁷⁹

3. Post-Section 401 of FDAMA: Where Are We Now?

On September 30, 2006, section 401 of FDAMA and its safe-harbor provision expired.⁸⁰ Serious criticism has surfaced,⁸¹ relaying similar concerns proponents of the 1997 amendments to the FDCA once made twelve years ago.⁸² Where only a short time ago section 401 of FDAMA provided a means to oversee the circulation of reputable promotional materials about off-label uses in order to “ultimately enhance the public’s health and safety” through FDA’s “opportunity to review, comment on, and approve articles” that were being circulated,⁸³ the newly published guidance seeks to serve as a substitute for the expired section 401 provision,⁸⁴ but its impact, so far, has not met approval. Although the current law

76. Cooper, *supra* note 75 at 488; FDA Guidance Document: Decision in Washington Legal Foundation v. Henney, 65 Fed. Reg. at 14,286–87.

77. Washington Legal Found. v. Henney, 128 F. Supp. 2d 11, 13 (D.D.C. 2000).

78. Stephanie Stapleton, *AMA: Science Must Be Key in Off-Label Drug Information* (Aug. 18, 1997), http://www.ama-assn.org/amednews/1997/pick_97/pick0818.htm.

79. O’Reilly & Dalal, *supra* note 70, at 302–05.

80. After Section 401 ceased to be in effect in 2006, two years passed before FDA released a draft guidance over the distribution of journal articles promoting off-label uses. See Notice of Availability, 73 Fed. Reg. 9342 (Feb. 20, 2008). The final guidance was published on January 13, 2009. FDA GOOD REPRINT GUIDANCE, *supra* note 9, at 1–2.

81. See *infra* Part III.A.2.

82. For example, Senator Edward Kennedy, during the floor debate over the 1997 proposed additions to the FDCA, stated that “companies are circulating articles without reviewing them for off-label uses, without seeking review or approval by the FDA, and without conducting the studies which would lead to an ultimate FDA approval or disapproval of the drug[’s use].” 143 CONG. REC. 19,836, 19,844 (daily ed. Sept. 24, 1997) (statement of Sen. Kennedy).

83. 143 CONG. REC. at 19,843–44.

84. FDA GOOD REPRINT GUIDANCE, *supra* note 9, at 1–2.

precludes any promotion of a drug for unapproved uses,⁸⁵ drug companies have widely distributed promotional articles for years and have been met with little to no consequence.⁸⁶

The controversy over the integrity and balance of off-label promotional practices, currently through the popular form of scientific, doctor-reviewed, journal reprints, has recently sparked further debate. Several cases have emerged in which pharmaceutical companies paid physicians to compose articles about the company's products in a favorable way, adding credence to the argument that drug companies may be focusing on promoting off-label uses rather than engaging in a peer-review process that objectively discusses a product's scientific effects.⁸⁷ Additionally, other recent instances have revealed that drug companies had sponsored unacknowledged authors to write promotional journal articles but attributed authorship to academics who had minutely contributed to the research and composition.⁸⁸ It is undeniable that the current behind-the-scenes focus by drug companies to manipulate physicians in prescribing drugs for off-label use must be curtailed. Full disclosure of conflicts of interest between drug companies and physicians may not be enough to assure a product's safety and efficacy. What is greatly needed is an evidence-based efficient regulatory review process that would aim at encouraging new medical treatments but in a manner that portrays a product's true therapeutic capability.

C. FDA's Other Efforts to Crack Down: Recent Developments in Off-Label Promotion

In addition to having the ability to charge drug companies for violations of the misbranding provisions within the FDCA, federal prosecutors also have available

85. Psaty & Ray, *supra* note 25, at 1949.

86. Scott Gottlieb, *From FDA, A Good Framework for Distributing Information on Off-Label Uses*, HEALTH AFFAIRS BLOG, Apr. 23, 2008, <http://healthaffairs.org/blog/2008/04/23/from-fda-a-good-framework-for-distributing-information-on-off-label-uses/> (arguing that the new guidance provides a good framework for the drug industry but that any further restrictions over the distribution of promotional material for off-label uses could hamper the development of medical products).

87. Joseph S. Ross et al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib: A Case Study of Industry Documents from Rofecoxib Litigation*, 299 JAMA 1800, 1806–10 (2008) (reporting that several industry-sponsored publications related to rofecoxib were authored independently by Merck & Co., Inc. before attributing authorship to medically affiliated practitioners or academics); see also Angela Spelsberg et al., *Is Disclosure of Potential Conflicts of Interest in Medicine and Public Health Sufficient to Increase Transparency and Decrease Corruption?*, 63 J. EPIDEMIOLOGY CMTY. HEALTH 603, 603–04 (2009) (suggesting the need and importance of disclosing conflicts of interest within the medical community and public health arena so as to increase transparency and legitimacy of commercially driven clinical research and studies); Ben Hirschler et al., *Merck Vioxx Study Was for Marketing: Researchers*, REUTERS, Aug. 19, 2008, available at <http://www.reuters.com/article/idUSLJ36290220080819> (noting that a 1999 clinical study of Vioxx was really tailored to encourage prescribing and not therapeutic applications or risks).

88. DeAngelis & Fontanarosa, *supra* note 10, at 1833 (reporting on two instances of explicit manipulation of clinical research articles and clinical reviews by industry-sponsored physician authors).

to them two other federal statutes to impugn both criminal and civil violations against manufacturers who promote off-label uses of their products: (1) the False Claims Act,⁸⁹ and (2) the Anti-Kickback statute.⁹⁰ Although doctors prescribe drugs for off-label medical treatment, drug companies can be held liable for off-label promotional activities if the promotional efforts induced health care practitioners to claim reimbursements for uses that Medicare and Medicaid do not provide coverage.⁹¹ The combination of doctors who regularly prescribe off-label⁹² with the risky business tactics some pharmaceutical companies engage in is significant, and by partaking in the practice of off-label promotion without some form of review, the existing hole in the regulatory system may very well lead to patients receiving ineffective treatments, or in some circumstances, adverse affects.⁹³

1. Warner-Lambert Co.'s Off-Label Promotion of Neurontin

Seemingly, the bottom line for the pharmaceutical industry's off-label promotion practices may just be all about money. In January 2004, the health care fraud unit of the U.S. Attorney's Office discovered that Warner-Lambert Co., a subsidiary unit of Pfizer, Inc. at that time, had engaged in a scheme to encourage physicians to prescribe Neurontin, a drug approved for treatment of epilepsy only, for a medical condition the FDA had never approved it for.⁹⁴ Pfizer reported \$2.27 billion in revenue from sales of Neurontin in 2002, and ninety-four percent of that profit, \$2.12 billion,⁹⁵ according to the prosecutors' 2004 Pfizer sentencing memorandum, was traced to off-label prescription use.⁹⁶

89. 31 U.S.C. §§ 3729–3730 (2006).

90. 42 U.S.C. § 1320a-7b (2006).

91. See, e.g., Stephanie Greene, *False Claim Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN ST. L. R. 41, 53–68 (2005) (evaluating the legal implications the False Claims Act and the Anti-Kickback statute can attribute against a drug company who engages in off-label promotion practices); Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J. L. SCI. & TECH. 61, 102–23 (2008) (noting the impact of the Neurontin litigation as an illustration of persistent off-label marketing and prescribing versus the need for objective clinical research and honest dissemination of new therapeutic uses).

92. David M. Fritch, *Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech from Drug Manufacturers on Off-Label Drug Treatments*, 9 MICH. ST. U. J. MED. & L. 315, 356 n.219 (2005) (“One estimate indicated off-label use accounted for 40–50% of the \$216 billion spent on U.S. prescription drugs in 2003.”); Maxwell J. Mehlman, *Off-Label Prescribing*, <http://www.thedoctorwillseeyounow.com/content/bioethics/art1971.html> (last visited June 20, 2010) (“[E]stimates [of off-label prescriptions] run as high as 60% of all drug prescriptions written in the United States in a given year . . .”).

93. See Dresser & Frader, *supra* note 3, at 482 (arguing that the failure to include children, pregnant women, and older people in clinical studies could deprive this class of the patient population from beneficial off-label therapies).

94. Evans, *supra* note 58, at 73.

95. *Id.* at 76.

96. Sentencing Memorandum of the United States, *United States v. Warner-Lambert Company LLC*, Criminal No. 04-10150 RGS (Mass. Dist. Ct., filed June 2, 2004), at 10–15.

After much negotiation, Warner-Lambert Co. pleaded guilty to two felony counts for violating the FDCA in connection with its misbranding of Neurontin when it failed to supply satisfactory directions for suggested usage and for introducing an unapproved drug into interstate commerce.⁹⁷ Pfizer arranged to pay \$430 million in criminal fines and civil health care liability penalties for Warner-Lambert Co., and in addition, agreed to abide by the terms of a corporate compliance program, which in essence, mandated Pfizer not only to make changes to Warner-Lambert Co.'s aggressive marketing tactics but also provide operative training and supervision to its marketing and sales staff in order to "ensure[] that any future off-label marketing conduct is detected and corrected on a timely basis."⁹⁸ The compliance program proved to be short-lived. Despite this, the Neurontin case established legal importance because the False Claims Act broadened the federal government's efforts in prohibiting off-label promotion by providing private individuals the ability to initiate legal actions, leaving pharmaceutical manufacturers to answer to financial exposure and negative publicity.⁹⁹

2. Pharmacia & Upjohn, Inc.'s Off-Label Promotion of Bextra

On September 2, 2009, another Pfizer subsidiary, Pharmacia & Upjohn, Inc., pled guilty to one felony violation of the FDCA for instituting an illegal scheme to promote Bextra for off-label use.¹⁰⁰ In this instance, Pfizer marketing executives directed more than 100 sales representatives to promote Bextra for various acute pain conditions and dosages that it had not been approved for in 2005.¹⁰¹ Several studies in 2005 revealed that the use of Bextra showed an increase of cardiovascular risk in specific types of medical treatment for which Pfizer executives had promoted the drug, and as a result, FDA refused to approve those Bextra uses on account of safety concerns.¹⁰²

97. See *id.* at 4–5 (evaluating what constitutes a misbranding violation). The FDCA prohibits the introduction of any misbranded drug into interstate commerce. 21 U.S.C. § 331(a) (2006).

98. Press Release, Dep't of Justice, 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.

99. Mello et al., *supra* note 50, at 1561–63.

100. Statement of Assistant Attorney General Tony West Before the Senate Judiciary Committee Entitled "Effective Strategies for Preventing Health Care Fraud" (Oct. 28, 2009), available at <http://www.justice.gov/dag/testimony/2009/dag-testimony-091028.html> [hereinafter Statement of Assistant Attorney General].

101. Evans, *supra* note 58, at 74. Bextra was a drug approved by the FDA only for the relief of arthritis and menstrual discomfort. *Id.* The FDA found Bextra to be so hazardous that Pfizer, Inc. took it off the market for all uses in 2005. *Id.* Therefore, the time period in which these Pfizer executives were active in pushing for off-label Bextra sales was approximately the same time when Pfizer, Inc. was resolving the criminal and civil liability allegations for illegally promoting Neurontin in 2004. *Id.*

102. Statement of Assistant Attorney General, *supra* note 100.

Pfizer was walloped with \$2.3 billion in fines and penalties.¹⁰³ Despite being the largest health care fraud settlement to date by the Department of Justice,¹⁰⁴ the \$2.3 billion in fines amounted to a mere 14% of Pfizer's \$16.8 billion in Bextra sales revenue from 2001 to 2008.¹⁰⁵ In addition to these fines and penalties, Pharmacia & Upjohn, Inc. was also directed to pay a criminal fine of \$1.195 billion and a criminal forfeiture of \$150 million, a total of \$1.3 billion in criminal fines, the largest criminal fines ever mandated in the United States.¹⁰⁶ Regardless of this record-breaking health care fraud enforcement effort, Pfizer has paid a total of \$2.75 billion in off-label penalties since 2004, but in crunching the numbers, this amounts to only 1.12% of the pharmaceutical giant's \$245 billion proceeds from 2004 to 2008.¹⁰⁷

There is no question as to whether there will be more such settlements; the significance here is when such settlements will be publicly announced and how large the fines and penalties will entail. For example, the first of these types of settlements for fiscal year 2009 publicly materialized in January 2009 when Eli Lilly & Co. plead guilty to violating the FDCA in order to settle charges alleging that the sizeable pharmaceutical company had, for no less than four years, illegally marketed Zyprexa, a drug the FDA had approved for the treatment of schizophrenia, for usage of dementia in elderly patients.¹⁰⁸ In a multi-site placebo-controlled trial studying the effects of Zyprexa for the treatment of dementia, out of the group of patients that were administered Zyprexa, 24%, the largest percentage compared to the other administered anti-psychotic drugs, had to discontinue their assigned treatment dosage due to adverse effects: intolerability to the drug, sedation, dizziness, cerebrovascular instances, extrapyramidal signs, and death.¹⁰⁹

3. It's Crunch Time: What Is the Lesson Here?

Due to the increased frequency of U.S. pharmaceutical companies pleading guilty to criminal charges and paying fines and penalties to resolve civil liabilities in the last decade for promoting FDA approved drugs for off-label use, often by deception or inducements to physicians, there is little doubt that pharmaceutical executives have increased marketing efforts in order to spur sales and create a new

103. *Id.*

104. *Id.*

105. Evans, *supra* note 58, at 74.

106. Statement of Assistant Attorney General, *supra* note 100.

107. Evans, *supra* note 58, at 74.

108. *Id.*

109. See Lon S. Schneider et al., *Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease*, 355 NEW ENG. J. MED. 1525, 1536-37 (2006) (concluding that given the large number of adverse effects of Zyprexa, also known as olanzapine, along with the other anti-psychotic drugs administered, the recorded efficacy, as a whole, was minimal).

market, that of off-label use, for existing FDA approved drugs.¹¹⁰ In promoting off-label uses for drugs that have neither been tested for efficacy or patient safety, the practice of promoting drugs for off-label use in such drastically high numbers to the public is putting millions of individuals at risk to a plethora of adverse and unknown effects. Any kind of promotion or circulation of information about an unapproved use of a drug should be conducted on a high academic and scientific level.¹¹¹ The test should consider whether the manufacturer of the drug product will monetarily benefit from the increased off-label use of the product as a result of the circulation of promotional materials. If so, some form of regulation should be necessary to oversee the content of the promotional materials so as to both protect and prevent serious harm to the public from use of such enormously active chemical products.

II. *UNITED STATES V. CARONIA*: AN EXAMPLE OF A PUBLIC HEALTH FOCUS IN OFF-LABEL PROMOTION

A New York district court ruling on a motion to dismiss served as a warning call to pharmaceutical manufacturers over their off-label promotional activities of products. In *United States v. Caronia*,¹¹² the Eastern District of New York considered whether Alfred Caronia, a sales representative of Orphan Medical, Inc., violated the FDCA when he marketed non-FDA approved uses of the drug Xyrem.¹¹³ In light of *Central Hudson Gas v. Public Service Commission of New York*,¹¹⁴ which articulates a four-part test for determining whether commercial speech is protected by the First Amendment, the court held that the misbranding provisions of the FDCA as applied to Caronia's activities in promoting Xyrem for off-label use were not an unconstitutional restriction of commercial speech under the First Amendment.¹¹⁵ In denying the pharmaceutical sales representative's motion to dismiss, the Eastern District of New York made several important interpretations about the First Amendment and its application to off-label promotion.¹¹⁶ In reaching its conclusion, the court held that the FDA's interest in safeguarding the public health outweighed Caronia's right to freedom of speech even though (1) the behavior Caronia sought to encourage—physicians prescribing a drug for off-label uses—is not illegal, and (2) the information Caronia used to promote off-label uses of Xyrem was neither false nor misleading.¹¹⁷

110. Psaty & Ray, *supra* note 25, at 1950–51.

111. Dresser & Frader, *supra* note 3, at 483.

112. 576 F. Supp. 2d 385 (E.D.N.Y. 2008).

113. *Id.* at 388–89.

114. 447 U.S. 557 (1980).

115. *Caronia*, 576 F. Supp. 2d at 393–401.

116. *See infra* Part II.B.

117. *Caronia*, 576 F. Supp. 2d at 401–02.

A. The Case

In July 2002, Orphan Medical, Inc., now known as Jazz Pharmaceuticals,¹¹⁸ received approval from the FDA to market Xyrem, a powerful sleep-inducing depressant to treat cataplexy, a condition associated with narcolepsy that causes one's muscles to stop functioning without notice.¹¹⁹ After submitting a Supplemental New Drug Application for Xyrem to the FDA, in November 2005, the FDA also approved Xyrem to treat narcolepsy patients suffering from excessive daytime sleepiness.¹²⁰ The FDA has only approved Xyrem for these two specific uses.¹²¹

Narcolepsy is a chronic neurological disorder that affects approximately 140,000 Americans.¹²² An estimated sixty to ninety percent of narcolepsy patients experience cataplexy,¹²³ a debilitating symptom of narcolepsy that is usually triggered by strong emotions such as laughter, anger, or surprise.¹²⁴ In the most severe cases, cataplexy causes one's muscles to tense up and stop functioning all together at any given moment, prompting a person to collapse during waking hours.¹²⁵ Because the trademark symptom of narcolepsy is excessive and overpowering daytime sleepiness, even after sleeping at nighttime, narcoleptics are often prescribed day time stimulants in order to stay awake and nighttime depressants to help one's body to sleep.¹²⁶

The active ingredient in Xyrem is gamma-hydroxybutrate, otherwise known as GHB, a powerful and fast-acting central nervous system depressant capable of inducing sleep in a short period of time.¹²⁷ Use of Xyrem has been reported to

118. Orphan Medical, Inc. is a Delaware corporation with its headquarters and principal place of business located in Minnetonka, Minnesota. Orphan is a specialty pharmaceutical company focused primarily on the development of drugs to treat pain, sleep disorders, and central nervous system disorders. Superseding Misdemeanor Information, United States, v. Gleason, Criminal No. 06-229 (S-2) (ENV) (E.D.N.Y. Aug. 8, 2008).

119. *UCB and Jazz Pharmaceuticals Announce Expansion of Xyrem(R) License Agreement to Include Fibromyalgia Syndrome*, MED. NEWS TODAY, Oct. 4, 2006, available at <http://www.medicalnewstoday.com/articles/53332.php> [hereinafter *UCB and Jazz Pharmaceuticals Expansion of Xyrem*].

120. Frederick R. Ball et al., *How Hard Should It Be to Imprison Someone for Telling the Truth?: FDA Advertising Regulation Enforcement*, UPDATE (Food & Drug L. Inst., Wash., D.C.), Sept./Oct. 2009, at 6, 8, available at <http://www.wlf.org/Upload/misc/pressclips/2009FoodDrugLawInstitute.pdf>.

121. *Caronia*, 576 F. Supp. 2d at 389.

122. *Orphan Medical Announces FDA Approval of Xyrem*, PROJECTGHB.ORG, July 17, 2002, http://www.projectghb.org/orphan_medical.htm.

123. *Id.*

124. *Id.*

125. *Id.*

126. *UCB and Jazz Pharmaceuticals Expansion of Xyrem*, *supra* note 119; see also Univ. of Maryland Med. Ctr., *Narcolepsy Treatment*, http://www.umm.edu/patiented/articles/what_treatments_narcolepsy_000098_6.htm (last visited June 20, 2010) ("Stimulant drugs are used to manage excessive daytime sleepiness while antidepressants and other compounds address cataplectic symptoms.").

127. *UCB and Jazz Pharmaceuticals Expansion of Xyrem*, *supra* note 119.

cause a number of potential side effects, such as difficulty breathing while asleep, confusion, abnormal thinking, depression, nausea, vomiting, dizziness, headache, bedwetting and sleepwalking.¹²⁸ In addition, clinical studies show that abuse of Xyrem can lead to dependence and severe withdrawal symptoms along with serious medical problems including seizures, coma, and death.¹²⁹ Due to concerns over Xyrem's serious dangers and potential abuse, FDA required Xyrem's label to incorporate a "black box" warning,¹³⁰ stating that Xyrem's safety and efficacy have not been ascertained for use by elderly and children patients.¹³¹

In April 2005, the FDA's Office of Criminal Investigations, Special Prosecutions Staff, began a criminal investigation of alleged off-label promotion of Xyrem by Orphan Medical and one of its sales representatives.¹³² During the investigation, the government utilized a physician as an undercover witness to verify if the allegations were true. On October 26, 2005, the government accused Caronia of advertising to the undercover physician several off-label uses of Xyrem for patients suffering from fibromyalgia, EDS, and chronic pain and fatigue.¹³³ The government also charged that, on November 2, 2005, Caronia introduced the undercover physician to an Orphan-paid physician who then subsequently promoted Xyrem for further off-label uses, including sleepiness, weight loss, and chronic fatigue.¹³⁴

The United States government filed a two count misdemeanor charge against Caronia for allegedly violating the FDCA's misbranding regulations.¹³⁵ Count one of the misdemeanor charge alleged that between March 2005 and March 2006, Caronia knowingly and intentionally conspired with others to misbrand a drug when he marketed Xyrem for off-label uses in violation of 21 U.S.C. §§ 331(a), (k), 333(a)(1), and 18 U.S.C. § 371.¹³⁶ Count two of the misdemeanor charge accused Caronia of partaking in a substantive violation of misbranding a drug while it was

128. *Id.*

129. *United States v. Caronia*, 576 F. Supp. 2d 385, 389 (E.D.N.Y. 2008).

130. *Id.* A black box warning is a specific type of warning that appears on a prescription drug's package insert. A black box warning serves as an alert to potential users that a drug carries a significant risk of harm. 21 C.F.R. § 201.57(c)(1) (2009).

131. *Caronia*, 576 F. Supp. 2d at 389.

132. *United States v. Caronia*, Superseding Indictment ¶¶ 12, 24(e).

133. *Caronia*, 576 F. Supp. 2d at 389.

134. *Id.* at 389–90.

135. *Id.* at 389. In July 2007, Orphan Medical plead guilty to felony charges pursuant to FDCA's misbranding provision and paid more than \$20 million in fines and penalties. Orphan Medical further admitted to engaging in a scheme to promote Xyrem for off-label uses through their sales representatives and physician consultants. On one occasion, for example, an Orphan Medical-paid psychiatrist advised other physicians on how to "conceal" Xyrem prescriptions from insurance reimbursement forms. Press Release, Jazz Pharmaceuticals, Inc. Agrees to Pay \$20 Million to Resolve Criminal and Civil Allegations in "Off-Label" Marketing Investigation (July 13, 2007), available at <http://www.justice.gov/usao/nye/pr/2007/2007jul13a.html>.

136. *Caronia*, 576 F. Supp. 2d at 389.

held for sale after shipment in interstate commerce, violating 21 U.S.C. §§ 331(k) and 333(a)(1).¹³⁷

Caronia moved to dismiss the misdemeanor charge on several grounds, arguing that the misbranding provisions of the FDCA violated his right to free speech under the Free Speech Clause of the First Amendment.¹³⁸ The *Caronia* court promptly rejected Caronia's first two arguments that were presented in support of his motion to dismiss.¹³⁹ The court then expended significant analysis on Caronia's First Amendment argument because the constitutional issues being raised by Caronia "are very much unsettled, not only in this circuit but nationwide."¹⁴⁰ Caronia presented the argument that the government, through its misbranding provisions of the FDCA cannot restrict truthful, non-misleading promotion by a pharmaceutical manufacturer to a physician with respect to off-label uses because such restrictions of commercial speech are unconstitutional.¹⁴¹ After a careful analysis of Caronia's First Amendment justification against FDCA's restrictions on promotion of off-label uses, the court rejected Caronia's argument, deciding that, in this circumstance, the FDCA's prohibition against encouragement of off-label uses is an appropriate, and constitutional, government exercise in light of its interest in protecting public health.¹⁴²

B. The Court's Reasoning

In *Caronia*, the Eastern District of New York denied Caronia's motion to dismiss charges of misdemeanor violations of the misbranding provisions of the FDCA and ruled that the case would proceed with jury selection and trial.¹⁴³ Writing for the court, Judge Vitaliano held the following: (1) that the information presented by the government was sufficient to allege violations of the misbranding provisions of the FDCA, (2) the alleged conduct by Caronia had in fact violated the FDCA, (3) the alleged promotion of off-label uses of Xyrem to physicians did constitute commercial speech under the First Amendment, (4) the misbranding

137. *Id.*

138. *Id.* at 393.

139. *Id.* Caronia first argued that the allegations in the indictment, and the supporting facts, actually illustrate that he did not misbrand Xyrem within the meaning of 21 U.S.C. § 331(k) because he provided sufficient verbal warning about the drug's side effects to the undercover physician. *Id.* at 391–92. The court rejected this argument and stated that it was "utterly without merit" based on the FDCA's "intended use" regulations. *Id.* at 392. Second, Caronia argued that he did not misbrand Xyrem in his conversations with the undercover physician because the physician he promoted off-label uses of Xyrem to was neither going to be a user or a prescriber of the drug. *Id.* The court also rejected this argument because 21 U.S.C. § 331(k) only requires the government to show that a defendant took some kind of action with respect to the misbranding of a drug. *Id.* The court further concluded that at the point of a case's motion to dismiss, a court must accept all factual allegations as true. *Id.* at 393.

140. *Id.* at 394.

141. *Id.* at 393.

142. *Id.* at 401–02.

143. *Id.* at 403.

provisions themselves did not violate the First Amendment protection for commercial speech, and lastly, (5) the misbranding provisions were not overbroad with regard to the scope and purpose of the FDCA's legitimate existence.¹⁴⁴ A summation of the court's analysis follows.

1. Can Caronia's Statements Be Considered as Commercial Speech?

The First Amendment disallows particular kinds of restrictions on freedom of speech. Nevertheless, not all forms of speech are granted the same level of protection.¹⁴⁵ In an attempt to interpret whether Caronia's conduct ought to have been constitutionally protected under the First Amendment's commercial speech doctrine, the court first considered whether the information promoting the off-label usage of Xyrem falls within the category of "speech" rather than that of "conduct."¹⁴⁶ Although the government argued that the commercial speech doctrine is not applicable in this instance because Caronia's acts of promotion only showed evidence of the intent element needed to establish criminal misbranding,¹⁴⁷ the court was unconvinced and further added that prior case precedent pointed to an alternative understanding of when acts constituted conduct and not speech, and vice versa.¹⁴⁸

The court next examined whether Caronia's alleged promotional acts of speech amounted to commercial speech. The court explained that their interpretation of when speech, here the promotional marketing acts by Caronia, corresponds with speech that can be categorized as falling under the commercial speech umbrella, would hinge upon an application of *Bolger v. Youngs Drug Products Corp.*'s three-factor test¹⁴⁹ that established when a promotional activity is deemed to be protectable within the ambit of commercial speech.¹⁵⁰ Applying the three factor test established in *Bolger*, the court then reached the conclusion that Caronia's statements to the undercover physician ought to be considered commercial speech because (1) the statements were in effect advertising Xyrem's potential use, (2) the statements in question is in regard to a specific product, Xyrem, and (3) the statements made were economically motivated.¹⁵¹ Thus, in applying the *Bolger* three factor test, the court reasoned that the promotional speech

144. *Id.* at 392–93, 395, 401–02.

145. *Id.* at 395–96.

146. *Id.* at 394–95.

147. *Id.* at 394 (citing *Whitaker v. Thompson*, 353 F.3d 947, 952–53 (D.C. Cir. 2004) (finding that the FDA did not violate the First Amendment's prohibitions on commercial speech when it concluded that a dietary supplement had to be approved as a drug before being marketed as effective)).

148. *Id.* at 395 (citing *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 59 (D.D.C. 1998) (stating that the FDA cannot consider the promotion of an activity as conduct and not speech)).

149. 463 U.S. 60, 63–68 (1983).

150. *Caronia*, 576 F. Supp. 2d at 396.

151. *Id.*

by Caronia to the undercover physician on behalf of Xyrem's manufacturer constitute commercial speech, and as such, should be "entitled to the qualified but nonetheless substantial protection afforded to commercial speech."¹⁵² After determining that Caronia's statements fall within the domain of commercial speech, the court then applied the *Central Hudson* test¹⁵³ to ascertain if Caronia's statements were protected by the First Amendment.¹⁵⁴

2. *Is the FDCA Misbranding Statute Unconstitutional Under Central Hudson?*

Having deduced that Caronia's promotional statements in marketing Xyrem to physicians amount to commercial speech, the Court next assessed whether Caronia's speech ought to be recognized as protected under the commercial speech doctrine of the First Amendment. To determine this, the Court applied the four-prong commercial speech test set forth in *Central Hudson*. In restating the *Central Hudson* test, the court summarized that its analysis must address the following four issues before reaching a conclusion: (1) whether the off-label speech at issue concerns lawful activity and is not inherently misleading, (2) whether the government has a substantial interest in restricting off-label promotion by manufacturers, (3) whether restricting off-label promotion by manufacturer directly advances a substantial government interest, and finally, (4) whether the "reasonable fit" test can be met when considering if FDCA's restriction of promoting off-label uses are not more extensive than necessary.¹⁵⁵ A synopsis of the court's analysis follows.

When embarking upon the *Central Hudson* test, the threshold issue that must first be addressed is whether Caronia's commercial speech statements constitute unlawful activity or if they are inherently misleading.¹⁵⁶ If Caronia's statements are determined to have been unlawful or misleading, then they are not afforded protection by the First Amendment and further application of the *Central Hudson* test is not needed.¹⁵⁷ Finding the Washington Legal Foundation cases to be persuasive, the court concluded that the promotional practices encouraging off-label uses is not itself unlawful or misleading.¹⁵⁸ Because physicians are permitted to prescribe drugs for off-label uses, the court contended that Caronia's statements about Xyrem's uses were therefore not illegal.¹⁵⁹ The court additionally found that Caronia's statements were not automatically misleading merely "because the use is

152. *Id.*

153. 447 U.S. 557, 566 (1980).

154. *Caronia*, 576 F. Supp. 2d at 396–402.

155. *Id.* at 396–97.

156. *Id.*

157. *Id.*

158. *Id.* at 397–98 (citing *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003); *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 66–67 (D.D.C. 1998)).

159. *Id.*

off-label.”¹⁶⁰ Since Caronia’s promotional statements were made to a physician who assumingly was familiar with the FDA drug approval process and because Caronia did not specifically assert that the uses he was promoting Xyrem for were FDA approved, the court then held that Caronia’s statements to the undercover physician were not misleading.¹⁶¹

Under the second prong of the *Central Hudson* test, the government must be able to assert a substantial interest behind a regulation.¹⁶² A court, then, must determine whether the asserted government interest is in fact substantial.¹⁶³ Relying on the *Washington Legal Foundation v. Friedman*¹⁶⁴ holding, the court emphatically noted that “the government had a substantial interest in promoting the health and safety of its citizens” and in order to reach that objective, “the government had a substantial interest in compelling manufacturers to get off-label treatments on-label.”¹⁶⁵ Although observing that the Supreme Court of the United States has previously held that paternalistic assumptions concerning the potential for the public to use truthful, non-misleading commercial information imprudently is not a justified reason for suppressing commercial information, the *Caronia* court still concluded that the government had a significant interest in encouraging manufacturers to participate in the FDA approval process of off-label uses of drugs.¹⁶⁶

After concluding that the government did indeed have a substantial interest in requiring off-label uses of drugs to be subjected to the FDA drug approval process, the third prong of the *Central Hudson* test a court must address is whether the regulation in question directly advances the government interest.¹⁶⁷ Relying once again on *Friedman* and *United States v. Caputo*,¹⁶⁸ the court asserted that “one of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising, and marketing.”¹⁶⁹ Because ultimately the audience of off-label uses of prescription drugs is now the public at large, the court observed that the impact of such uses has increased, giving credibility to the importance of labeling and advertising of these

160. *Id.* at 397.

161. *Id.* at 397–98 (quoting *United States v. Caputo*, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) (discussing the sophistication of the audience to whom the off-label uses were advertised)).

162. *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm’n of N.Y.*, 447 U.S. 557, 564 (1980).

163. *Caronia*, 576 F. Supp. 2d at 397–98.

164. 13 F. Supp. 2d 51 (D.D.C. 1998).

165. *Caronia*, 576 F. Supp. 2d at 398 (citing *Friedman*, 13 F. Supp. 2d at 69–71).

166. *Id.*

167. *Id.* at 397–98.

168. 288 F. Supp. 2d 912 (N.D. Ill. 2003).

169. *Caronia*, 576 F. Supp. 2d at 398 (citing *Caputo*, 288 F. Supp. 2d at 921; *Friedman*, 13 F. Supp. 2d at 72).

products.¹⁷⁰ Consequently, the court found that the “FDCA’s prohibitions on commercial speech of the kind charged in the information filed against Caronia directly advance the government’s interest in subjecting off-label uses of a drug like Xyrem” to the FDA’s drug evaluation and approval processes.¹⁷¹

In considering prong four of the *Central Hudson* test, the court then evaluated whether the FDCA’s misbranding provisions were not more extensive than necessary.¹⁷² To determine if the FDCA’s misbranding provisions were too extensive or appropriate, the court looked to several prior cases for reference.¹⁷³ Differentiating *Friedman* and *Caputo*, the *Caronia* court noted that Caronia’s First Amendment challenge directly confronts “FDA’s ability to proscribe manufacturer promotion of off-label uses.”¹⁷⁴ Because FDA’s ability to evaluate the effectiveness of off-label uses is severely frustrated and because the difficulty in identifying a less burdensome alternative that would advance the government’s substantial interest was present in Caronia’s circumstances, the court held that the FDA’s restriction on off-label speech were not more extensive than necessary, and as a result, the FDCA misbranding provisions satisfied the last element of the *Central Hudson* test.¹⁷⁵

C. Applying the Law and a Public Health Approach: Why the Caronia Court Has Been Right . . . So Far

As it currently stands, *Caronia* could make it more difficult for drug and device manufacturers to prevail on a First Amendment defense in promotion of off-label cases, and for good reason. FDCA’s misbranding provisions restricting off-label promotion of drugs are necessary to ensure that new uses for drugs are evaluated through its drug efficacy process, but participating in FDA’s drug approval process in relation to an off-label use is currently not mandatory.¹⁷⁶ Although drug companies may purport to be only passing truthful, non-misleading

170. *See id.* (stating that drugs subject to off-label prescriptions are already in interstate commerce, which limits how the FDA can influence manufacturer behavior).

171. *Id.*

172. *Id.* at 399–402.

173. *Id.* (citing *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 369–73 (2002) (analyzing a ban on advertising by pharmacies on compounded drugs under the four pronged test of *Central Hudson*); *Caputo*, 288 F. Supp. 2d at 919–22 (holding that FDA’s prohibitions against promoting non-FDA-approved uses via its misbranding provisions were not more extensive than necessary under prong four of *Central Hudson*); *Friedman*, 13 F. Supp. 2d at 59, 72–74 (discussing whether restrictions in FDA-issued Guidance Documents pertaining to the distribution of promotional materials and sponsorship of CMS seminars encouraging off-label uses are more extensive than necessary, thus rendering them unconstitutional)).

174. *Id.* at 399 (quoting *Caputo*, 288 F. Supp. 2d at 922).

175. *Id.* at 401–02.

176. *See Ratner & Gura, supra* note 20, at 871–72 (discussing the major reasons why drug developers are less inclined to file with the FDA supplemental approval applications to include off-label uses on an already FDA-approved label).

information to physicians, the safety and efficacy of these off-label uses have not undergone systematic evaluation.¹⁷⁷ And even though some drug companies report their clinical study results of off-label uses as being favorable for use, recent cases of manufacturers manipulating the results, by omitting indicia of ill-effects, have surfaced.¹⁷⁸

And so, even when promotional information is casted to a sophisticated listener, such as a practicing physician, the information about an off-label use should at least be considered as being uncertain.¹⁷⁹ Those against FDA's misbranding provisions restricting off-label promotion who argue that the government regulations restrict the free flow of commercial information are correct; but the restriction is not absolute. Drug manufacturers are not being restricted altogether from engaging in the dissemination of information for research and development of new uses for its products. Rather, drug companies are being instructed on how to participate commercially within such a highly regulated, and potentially dangerous, trade. Rules dictating the proper manner of engaging in the business of providing drugs is essential to protect the health and safety of the public, and without these policies, the quality of healthcare could ultimately plummet.¹⁸⁰

The impact of the *Caronia* decision provides a general understanding of the constitutional infirmities some argue FDA policy entails. But more importantly, the court validated the current regulatory scheme in restricting off-label promotion,¹⁸¹ leaving drug and medical device manufacturers to create alternative non-speech restrictive policies designed to be in compliance with FDA's regulatory interests.¹⁸² Maintaining control over new uses of regulated products is not always dependent upon assuring the actual truth or falsity of promotion speech. Ultimately, there is a distinction between commercial speech and scientific-based expression. FDA's role ought to be evaluating promotional speech impact to safeguard the public health from preventable risks in the context of off-label uses.¹⁸³ As the use of a

177. Dresser & Frader, *supra* note 3, at 477.

178. Psaty & Ray, *supra* note 25, at 1949–50.

179. See Largent et al., *supra* note 21 (suggesting several different ways a doctor ought to scrutinize available clinical evidence before prescribing off-label treatments).

180. See, e.g., Stafford, *supra* note 46, at 1427–29 (discussing the damaging results off-label use currently produces).

181. See *supra* Parts II.A, B.

182. See, e.g., A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers' First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439, 440, 454–61 (2003) (evaluating various speech-restrictive policies FDA has established related to off-label promotion and the tensions that exist between FDA's regulatory duties and the pharmaceutical industry's claim to commercial free speech in relation to its scientific information about their products).

183. See Psaty & Ray, *supra* note 25, at 1949–50 (arguing that FDA's recent guidelines allowing sponsors of pharmaceutical products to distribute publications about off-label uses lacks procedural safeguards that keeps the protection of the public health intact).

prescription drug changes, so too does its safety and efficacy.¹⁸⁴ By permitting drug manufacturers to advertise off-label uses, either through a physician or to the general public, the impending harm to the public's health and safety will become a reality.¹⁸⁵

Drug manufacturers should be urged, whether by regulation or by instituting a safe-harbor exception, to submit new drug applications for off-label uses to the FDA. While the advantages of off-label prescribing consist of earlier accessibility of life-saving treatments, new generations of medical innovations, and decreased drug costs in part from side-stepping FDA's expensive and time-consuming standard approval process,¹⁸⁶ the disadvantages heavily outweigh the gains. The risks to public health and safety and the current efforts to encourage physicians to prescribe off-label uses come at a time where drug manufacturers have realized large profits. By influencing the prescribing habits of physicians, drug manufacturers will have decreasing incentives for participating in the FDA's drug approval process. A concern for the *Caronia* court, it hypothesized that if FDA's current prohibitions against promotion of off-label uses did not exist, drug manufacturers would have no incentive from obtaining a drug approval for a certain use, and then turning around to promote that same drug for off-label uses.¹⁸⁷ This is only one projected problem that could arise but it is one that serves as an example of how off-label promotion is inextricably connected to commercialism and public health.

To promote safe and efficacious uses of off-label medication, FDA policymakers should seek to create prospective policies that could help inform the development of balanced opinions and procedures that the industry, physicians, consumers, and government could then use to make judgments about off-label uses.¹⁸⁸ The FDA must design their enforcement policy in a way that would lessen the drug manufacturer's practices of providing unchecked information to physicians. Complete restriction of a drug industry's participation in engaging in commercial speech is not, nor should it ever be, the effect of the government's regulation of off-label promotion. The aim of government off-label regulations should encourage transparency and support for the monitoring of off-label use so

184. Dresser & Frader, *supra* note 3, at 477.

185. See, e.g., Ausness, *supra* note 11, at 1256–96 (discussing various forms of liability drug companies can face for violating either the FDA's restrictions on the marketing of off-label uses or other health care fraud laws).

186. Muriel R. Gillick, *Controlling Off-Label Medication Use*, 150 ANNALS OF INTERNAL MED. 344, 344 (2009).

187. *United States v. Caronia*, 576 F. Supp. 2d 385, 401 (E.D.N.Y. 2008).

188. See Dresser & Frader, *supra* note 3, at 483 (proposing various recommendations on how to oversee off-label promotional activities by engaging FDA policymakers, Congress, and physicians together to hone-in on improving current inappropriate practices of off-label prescribing).

that the practice of off-label promotion is actually enhancing public health and patient care, and not exploiting the use of novel medicines.¹⁸⁹

One provision FDA could consider enacting is a provision that mandates safety and efficacy clinical research of an off-label use product once that off-label use has either (1) reached a certain threshold revenue or (2) has surpassed a specific number of prescriptions issued.¹⁹⁰ Although at first glance, tracking such statistics may require additional resources and manpower, this would provide the FDA an additional way to monitor the most frequently issued off-label uses of drugs while simultaneously promoting the participation of FDA's drug approval process. This way, the new beneficial innovations that come with certain off-label uses could be reinforced through government oversight, creating a collaborative effort between the government and the medical profession in together striving to provide patients with the best and safest care. Drug companies should acknowledge that FDA's restrictions of drug promotional claims are "not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media."¹⁹¹ FDA's focus is maintaining low risks to public health and safety, and in order to achieve this, off-label use should be deemed as a public health concern.¹⁹² The *Caronia* court implicitly acknowledged this application of public health to off-label promotion; so too should the FDA and the pharmaceutical industry.

Whether the *Caronia* decision validating the current regulatory scheme in restricting off-label promotion will continue to stand is uncertain. Subsequent to the court's motion to dismiss ruling, a jury in the U.S. District Court for the Eastern District of New York convicted Alfred Caronia of conspiring to promote the narcolepsy drug Xyrem for off-label use.¹⁹³ Recently, Caronia filed a brief in the U.S. Court of Appeals for the Second Circuit and argues that because he did not communicate anything false about the drug or the manner in which doctors use the drug when treating medical conditions, he ought to be protected by the First

189. See Jane E. Henney, *Safeguarding Patient Welfare: Who's in Charge?*, 145 ANNALS OF INTERNAL MED. 305, 306 (2006) (urging physicians and academic institutions to facilitate transparent communications with the pharmaceutical industry so that industry-sponsored research and publications maintain objectivity in its main efforts to provide quality patient care and worthwhile drug development research).

190. CTR. FOR HEALTH & PHARM. LAW & POL'Y, SETON HALL UNIV. SCH. OF LAW, DRUG AND DEVICE PROMOTION: CHARTING A COURSE FOR POLICY REFORM 15 (2009), available at http://law.shu.edu/ProgramsCenters/HealthTechIP/upload/whitepaper_jan2009.pdf.

191. 21 C.F.R. § 312.7(a) (2009).

192. See generally Christopher D. Zalesky, *Pharmaceutical Marketing Practices: Balancing Public Health and Law Enforcement Interests; Moving Beyond Regulation-Through-Litigation*, 39 J. HEALTH L. 235, 243 (2006) (arguing that FDA should have a more expanded role in overseeing pharmaceutical marketing practices because the consequences of misleading sales practices lead to over-utilization of medical treatments and adverse effects to patients).

193. David Belian, *Defendant Cites First Amendment in Off-Label Promotion Case*, DRUG INDUSTRY DAILY, Apr. 28, 2010.

Amendment from being prosecuted for imparting truthful statements about a commercial product.¹⁹⁴ The appellate court has not yet scheduled a date to hear oral arguments.¹⁹⁵

III. A CRITIQUE OF FDA'S GUIDANCE ON GOOD REPRINT PRACTICES AND PUBLICATIONS

On January 13, 2009, FDA announced the publication of its final version of guidance for *Good Reprint Practices for the Distribution of Medical Journal Articles or Scientific Reference Publications* on off-label uses.¹⁹⁶ After section 401 of FDAMA ceased to be effective in September 2006,¹⁹⁷ FDA issued this final non-binding guidance on Good Reprint Practices intending to clarify the policy governing one aspect of off-label marketing, the agency's current view on the dissemination of medical and scientific publications on off-label use.¹⁹⁸ Reaction to FDA's final guidance has been mixed.¹⁹⁹ One significant change, at a minimum, has sparked strong criticism: that of not requiring drug companies to submit a new drug application for off-label uses discussed in the disseminated materials.²⁰⁰ This omission, along with other key implications of the final guidance, will not provide an adequate medium to address broad public health concerns about off-label promotion, and further, it could weaken FDA's overall influence in promoting efficacy and safety practices.²⁰¹

A. Summary of FDA's Final Version

The guidance released in January 2009 presents guidelines for drug companies on how to disseminate scientific and medical publications in a manner that would not violate the federal ban against promotion of unapproved uses for drugs and devices. The guidance permits the distribution of peer-reviewed scientific articles that describe various off-label uses, but this allowance is subject to several conditions.²⁰² A summary of the types of publications FDA will permit and the method in which the off-label information should be distributed follows.

Under the guidance, a scientific or medical journal publication that is distributed should meet the following requirements:

194. Amicus Curiae Brief of Washington Legal Found. in Support of Appellant Alfred Caronia and Reversal, No. 09-5006-CR (2d Cir. Apr. 22, 2010), at 5–30.

195. Belian, *supra* note 193.

196. 74 Fed. Reg. 1694 (Jan. 13, 2009).

197. 21 U.S.C. § 360aaa (2006).

198. FDA GOOD REPRINT GUIDANCE, *supra* note 9, at 1.

199. *See infra* Parts III.B, C.

200. *See infra* Part III.A.2.

201. Psaty & Ray, *supra* note 25, at 1949.

202. Dresser & Frader, *supra* note 3, at 482.

- (1) Be published by an organization that has an editorial board that utilizes experts in the subject of the article under review and who are independent of the organization to review . . . and that has a publicly state policy, to which the organization adheres, full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- (2) Be peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- (3) Not be in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.²⁰³

The guidance also clearly provides instances where scientific or medical reference articles should not be distributed.²⁰⁴ The guidance states that these types of journal articles should not be disseminated if the literature is primarily distributed by a drug or device manufacturer, is composed, edited, or excerpted specifically for a drug or device manufacturer, or composed by individuals who have a financial relationship with the manufacturer.²⁰⁵ The guidance insists that the information being disseminated must not be false or misleading, inconsistent with credible evidence, or pose significant risk to the public's health.

Several guidelines providing instruction on the manner in which to disseminate scientific and medical information is also set forth in the guidance, and some are provided below:

- (1) Be in the form of an unabridged reprint, copy of an article, or reference publication;
- (2) Not be marked, highlighted, summarized, or characterized by the manufacturer in any way;
- (3) Be accompanied by the approved labeling for the drug or medical device;
- (4) Be distributed separately from information that is promotional in nature²⁰⁶

The guidance also provides a suggested list of affixed statements that should be accompanied when a journal reprint or reference publication is disseminated, but the language of the guidance in this section is only suggestive in nature, not mandated.²⁰⁷

203. FDA GOOD REPRINT GUIDANCE, *supra* note 9, at 4–6.

204. For a complete list of the requirements for disseminating scientific or medical publications as suggested by the FDA, see *id.* at 3–6.

205. *Id.* at 4.

206. *Id.* at 4–5.

207. *Id.* at 1, 5–6.

1. Proponents of the FDA's Guidance

In an effort to organize and express support for the recent guidance, a coalition of ten pharmaceutical companies joined patient advocacy groups to further their position.²⁰⁸ Among the several arguments in favor of the guidance, the need to preserve the information flow from drug manufacturer to the consumer is of utmost importance.²⁰⁹ According to supporters, by relaxing off-label marketing restrictions, drug companies will be better equipped to serve the needs of consumers in an efficient and faster rate than FDA would normally allow them to if they were absolutely restricted from engaging in off-label promotion.²¹⁰ This way, as new uses develop for already FDA-approved drugs, drug companies can continue to issue up-to-date therapeutic options for the benefit of a patient²¹¹ without the worry that FDA will automatically respond by filing FDCA misbranding charges.

Supporters of the guidance also contend that the new guidelines further public health initiatives. Pharmaceutical Senior Vice-President Ken Johnson reasoned, "The FDA guidance supports the public health by helping to assure that medical professionals receive timely and accurate medical information prior to the lengthy process for inclusion in the FDA-approved labeling."²¹² Because the guidelines themselves provide adequate suggestions on how to properly distribute informational materials to physicians, supporters argue that no further regulation is needed seeing as they are contributing to the overall development of medical treatment. Since the guidance does not impose mandatory restrictions on disseminating publications promoting off-label uses, providing only suggestions, the drug industry generally endorsed the guidance.²¹³

2. Opponents of the FDA's Guidance

The guidance has received stern criticism. House Representative Henry Waxman, one of the leading critics of the guidelines, commented that the guidelines are a "long-coveted parting gift" for the pharmaceutical industry that "fundamentally undermines" FDA's authority.²¹⁴ Critics assert that the omission of

208. Alicia Mundy, *Off-Label Use of Drugs Gets a Push—Big Pharma Lobbies Washington to Relax Rules on Marketing*, WALL ST. J., Apr. 18, 2008, at A14.

209. *Id.*

210. Gottlieb, *supra* note 86.

211. See Largent et al., *supra* note 21, at 1746–47 (arguing that off-label medical treatments are sometimes prescribed for different therapeutic purposes, and as a result, physicians should be well-versed in off-label uses to make certain the health benefits of the treatment is the most appropriate).

212. *FDA Final Guidance Permits Reprints of Articles of Off-Label Use*, DRUG INDUSTRY DAILY, Jan. 13, 2009.

213. Tribune McClatchy, *Bush, FDA Changed Rules to Benefit Off-Label Drugs*, BALTIMORE SUN, Feb. 1, 2009, at 13A.

214. *Id.*; see also Letter from Henry A. Waxman, House of Representatives to Andrew C. von Eschenbach, Comm'r, U.S. Food & Drug Admin. (Sept. 17, 2008) (on file with author) (reiterating

not requiring companies to submit a new drug approval application for off-label uses discussed in the disseminated scientific materials, a key requirement that was in effect under section 401 of FDAMA, effectively undercuts FDA's drug approval process.²¹⁵ Pointing to current and potential weaknesses in the integrity of scientific findings on drugs and devices, critics believe that the guidelines will not create the needed transparency between drug manufacturers and the promotional materials they distribute.²¹⁶ The fear that critics currently have over the present form of the guidance is that the objective research element inherent to a drug's safety and efficacy is being muddled and manipulated, and therefore, promotional journal publications ought to be viewed as suspect by the time they reach physicians and consumers.²¹⁷

There is no dispute that some off-label uses can be helpful in treating medical conditions. But what critics to the guidelines emphasize is that the practice of promoting off-label uses to large groups of consumers can be very dangerous.²¹⁸ Nearly every drug has side effects, some of them serious. Those risks consumers take can be worth the potential benefit when they are evaluated and properly studied. With off-label uses, on the other hand, the risks remain but the benefits are considerably less certain.²¹⁹ Because the guidance lacks any recommendation encouraging manufacturers to work towards submitting for FDA approval of the off-label uses endorsed in the promotional reprints, critics contend that manufacturers will opt not to conduct thorough clinical trials of off-label uses, may choose to mainly publish auspicious findings, and may perhaps portray study results in a manner that promotes their products favorably without any checks to

numerous concerns regarding FDA's guidance, urging the agency to re-examine the potential implications of publishing a final version of the guidance); Letter from Henry A. Waxman, House of Representatives to Andrew C. von Eschenbach, Comm'r, U.S. Food & Drug Admin. (Jan. 22, 2008) (on file with author) (conveying various concerns over the draft version of FDA's guidance on promoting off-label uses in medical journal articles); Ed Silverman, *Waxman to FDA: Watch Those Journal Articles*, PHARMALOT.COM, Nov. 30, 2007, available at <http://www.pharmalot.com/2007/11/waxman-to-fda-watch-those-journal-articles/> (reporting Representative Henry Waxman's reaction to FDA's guidance on promoting off-label uses in medical journal articles).

215. Comments to *Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, FDA Dkt. No. FDA-2008-D-0053, <http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2008-D-0053> (last visited June 20, 2009).

216. Jerome Kassirer, *Fantasy at FDA: Protecting the Public from Drug Company Reprints*, HEALTH AFFAIRS BLOG, Apr. 23, 2008, <http://healthaffairs.org/blog/2008/04/23/fantasy-at-fda-protecting-the-public-from-drug-company-reprints/>.

217. Bruce M. Psaty & Richard A. Kronmal, *Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment: A Case Study Based on Documents from Rofecoxib Litigation*, 299 JAMA 1813, 1813, 1816-17 (2008); Psaty & Ray, *supra* note 25, at 1949-50.

218. Chris Adams, *Late Move on Drugs by Bush FDA Could Be Dangerous*, MCCLATCHY NEWSPAPERS (WASH. D.C.), Feb. 1, 2009.

219. McClatchy, *supra* note 213.

the products' safety and efficacy.²²⁰ With safety profiles of off-label uses being uncertain, off-label promotion to physicians does not ensure that the quality of data being presented cannot be subject to major manipulation.²²¹

B. How the Guidance Should Be Reworked: The Lesson Here Is Lessen Risk

The potential for abuse by the pharmaceutical industry, given its record, is high. The public should reasonably be skeptical about the companies' marketing tactics in encouraging doctors to prescribe for off-label uses.²²² The danger to human safety by the increasing number of off-label prescriptions is real. New York State health commissioner, Dr. Richard F. Daines, wrote to FDA about his concerns of possible pharmaceutical industry manipulation of peer-reviewed journals, and stated, "We just have so many concerns You don't know the publication's true peer-reviewed standards and transparency."²²³ Proper precautionary efforts should be in place to prevent harm to patients and ensure that measures are taken to show that a medical product is truly effective, safe, and beneficial to population health. The value of encouraging the pharmaceutical industry to submit to the FDA an application for drug approval should be emphasized, helping to legitimize the process and establish accountability and trust for its disseminated promotional materials.

Ultimately, the focus for public policy here should center on how to encourage pharmaceutical companies to engage in non-misleading promotional efforts of their manufactured products. With each case of deceitful off-label marketing, millions of patients are unknowingly put at risk when physicians have been discovered to have prescribed medications based on skewed marketing ploys by drug companies and their employees.²²⁴ Although physicians do need to obtain information about potential new uses of medical products, physicians largely learn

220. CTR. FOR HEALTH & PHARM. LAW & POL'Y, *supra* note 190, at 14.

221. Frederic R. Curtiss & Kathleen A. Fairman, *Contradictory Actions on Off-Label Use of Prescription Drugs? The FDA and CMS Versus the U.S. Justice Department*, 15 J. MANAGED CARE PHARMACY 161, 162 (2009).

222. *See, e.g.*, Press Release, U.S. Food & Drug Admin., FDA Acts to Halt Marketing of Unapproved Codeine Sulfate Tablets: Four Companies Required to Stop Making and Distributing Illegal Opioid Pain Relievers (Oct. 13, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm186418.htm>; Press Release, U.S. Food & Drug Admin., FDA Warns of Potential Serious Side Effects with Breakthrough Cancer Pain Drug (Sept. 26, 2007), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108994.htm>. Recent FDA advisory panels have systematically reviewed frequent off-label uses and found them to be so lacking in efficacy or dangerous that either mandatory cessation in the marketing of an unapproved use of a drug was ordered or stern recommendations were issued to modify a drug's label with the aim of appending written warnings against the off-label use of a particular product. *Id.*

223. Stephanie Saul, *FDA Plan on Medical Articles Takes More Heat*, N.Y. TIMES, Apr. 19, 2008, at C3.

224. David Evans, *When Drug Makers' Profits Outweigh Penalties*, WASH. POST, Mar. 21, 2010, at G1.

about new uses from pharmaceutical-sponsored sources and these commercial efforts have been exceedingly effective in influencing many therapeutic decisions.²²⁵ Completely restricting off-label promotional efforts is not the reply policymakers should retort with since off-label uses of FDA approved products have and will continue to bring about new therapeutic treatments for patients. But entering the commercial market with these particular chemically compounded products should come with a heightened level of oversight by both the government and by the medical community. The purpose of passing off-label information along to physicians ought to facilitate ideas and knowledge to serve therapeutic good not pursue the engagement of the medical community to achieve commercial distribution of a product.²²⁶ What the FDA and the medical community must do is to take the cue from the *Caronia* court. The real emphasis of these guidelines should have been the public's health and since the guidelines provide substantial leeway for the dissemination of off-label uses without appropriate oversight, the configuration of the guidance is simply way too broad.

CONCLUSION

In light of the recent holding by the *Caronia* court, the FDA's current approach to restricting off-label promotional practices are constitutionally sound. Moreover, the court correctly emphasized that they are good policies that take into account FDA's role in managing and protecting the public's health from illness and industry abuse.²²⁷ However, FDA's prohibitions on off-label promotion, codified by its recent issuance of the guidance, does very little to encourage drug companies to participate in the new drug approval process. FDA acknowledges that physicians legally prescribe drugs for off-label uses to their patients on a regular basis. FDA also agrees that the use of unapproved treatments of drugs can sometimes be the standard of care for medical treatment to a particular group of patients. Nevertheless, restrictions upon manufacturers who distribute what they call truthful, non-misleading materials that encourage off-label uses, ought to be implemented given the recent trend by drug companies of dispensing promotional publications about products that have not been proven to be safe or effective, in addition to being highly dangerous and dependent-forming when consumed.²²⁸ The free flow and exchange of truthful information is paramount within our society but in the context of this heavily regulated industry, drug companies are not simply exchanging ideas and research. When a principal aim is to increase revenue at the

225. Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1729 (2008).

226. *See id.* at 1730–31 (suggesting that more oversight is needed of promotional statements by pharmaceutical manufacturers because the nature of the products being promoted have substantially influenced a physician's prescribing practices).

227. *See supra* Part II.C.

228. *See supra* Part I.C.

expense of the public's health, regulation is appropriate to ensure the public's ability in assessing relevant and safe medical treatment options.

Also of importance, by holding drug companies and their employees accountable for circulating egregious promotional materials that encourage off-label uses, not only will the public benefit be enhanced but the medical profession, too, will be improved by being better informed about what is truly a novel medical treatment option versus a marketing ploy disguised as scientific based reports. Although critics argue that FDA's enforcement efforts are repressing useful medical knowledge, if pharmaceutical companies were urged to participate in FDA's new drug approval process, by way of an updated safe-harbor provision, both FDA and the industry would be working collaboratively towards ensuring the information about an off-label use is actually reliable and factually complete. As it currently stands, and what the *Caronia* court stressed in its holding, the disarray that exists between a manipulated piece of literature and a scientifically grounded article justifies FDA's authority in limiting access to information related to off-label uses. The focus here is not absolute restriction, rather, it is the need to ensure whether the value being promoted to the public about an off-label use is precisely what it entails, and not merely what it seems.

