After *Caronia*: First Amendment Concerns in Off-Label Promotion

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I. INTRODUCTION

When a physician prescribes a drug or uses a medical device, most patients would assume that the drug or device has been approved by the Food and Drug Administration (FDA), the government agency charged with protecting consumers from unsafe and fraudulent foods and drugs.[1]

1. The FDA regulates the safety and efficacy of food, drugs, medical devices, and cosmetics. This Article focuses on the FDA's role in regulating the pharmaceutical industry and the marketing of drugs and devices. The FDA's mission regarding drugs and medical devices is described as promoting the public health "by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and "ensuring that . . . human and veterinary drugs are safe and effective." Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 393(b) (2012). The FDA derives its authority to regulate drugs and medical devices from several statutes. The Federal Food, Drug, and Cosmetic Act (FDCA) was passed in 1938 after a toxic elixir killed more than 100 people, including many children. *See* Efthimios Parasidis, *Patients Over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 2011 WIS. L. REV. 929, 937–40. The FDCA requires evidence of the safety of new drugs before they can be marketed. *See* Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence To Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299, 299 (2003). The Kefauver-Harris Amendments of 1962 required that drugs be proven not only safe but effective. *Id.* at 300. The FDA conducted a Drug Efficacy Implementation Study to

When the FDA approves a drug or device and its label, it does so for a particular use, or *indication*.[2] Frequently, however, a physician may prescribe a drug or use a device for something other than the FDA approved indication. Such practices are not illegal because the FDA does not regulate the practice of medicine.[3] If a physician prescribes a drug for an indication that has not been approved by the FDA, or for a dosage different than that approved by the FDA, the prescription is often referred to as "off-label."[4] Off-label prescribing by physicians is completely different from off-label marketing by pharmaceutical companies. Although patients may trust the judgment of their physicians to make prescribing decisions about off-label use, the promotion of drugs for off-label use raises controversial questions.[5]

The FDA discourages off-label promotion because the practice allows manufacturers to evade scientific evaluation of safety and efficacy. Representative Henry A. Waxman emphasizes that Congress has passed laws and regulations regulating information about drugs because without such regulations history has shown that "deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives."[6] Although companies maintain that the information they provide physicians is truthful, it is likely that they do not provide the

review pre-1962 drug claims and found that one-third of all drugs on the market "could not be shown to be effective for a single indication and had to be taken off the market." *Id.* at 304. The drugs included some of the most widely promoted and best selling drugs. *Id.* The Medical Device Amendments (MDA), added in 1976, regulate the safety and effectiveness of medical devices. Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (codified as amended at 21 U.S.C. §§ 351–360n-1 (2012)). The MDA responded to findings that faulty medical devices have caused numerous injuries and deaths. S. REP. NO. 94-33, at 6 (1975).

2. When the FDA approves a new drug, the approval only extends to the conditions indicated on the FDA-approved labeling. The FDA considers any alterations of the label, including recommending or suggesting a new use for the drug, to be a "new drug." 21 U.S.C. § 321(p) (2012). If the manufacturer seeks to introduce the drug into interstate commerce for a new use, it must seek and obtain FDA approval for that new use. 21 U.S.C. § 355(a) (2012).

3. The FDCA states, "Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." 21 U.S.C. § 396 (2012).

4. *See* Jane E. Henney, *Safeguarding Patient Welfare: Who's in Charge?*, 145 ANNALS INTERNAL MED. 305, 305 (2006).

5. *See infra* note 28.

6. Waxman, *supra* note 1, at 299.

whole truth and that information is frequently presented in a manner that is inherently fraudulent or misleading.[7] Furthermore, the government maintains that a physician's decision to prescribe a drug for an off-label use should not be influenced by a marketing campaign orchestrated to impact the physician's decision. Following a settlement with Eli Lilly in connection with both criminal and civil charges for off-label promotion of its drug Zyprexa, a U.S. Attorney stated that by ignoring the government's process for drug approval, companies "undermine the integrity of the doctor-patient relationship . . . . People have an absolute right to their doctor's medical expertise, and to know that their health care provider's judgment has not been clouded by misinformation from a company trying to build its bottom line."[8]

Despite FDA concerns, off-label marketing has been described as "so common among drug and device makers that it's often dismissed as the equivalent of driving slightly over the speed limit."[9] In fact, studies suggest that more than twenty percent of prescriptions are written for off-label uses.[10] Pharmaceutical companies and their supporters emphasize the benefits of off-label prescribing and the need for off-label promotion.[11] Advantages of off-label prescription include delivery of needed new treatments sooner rather than at the end of a lengthy and costly approval process.[12] Supporters also maintain that off-label promotion allows the company, which has the most complete information about the product, to give accurate, timely information to physicians.[13] Although off-label

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7. *See infra* Part IV.B.

8. Press Release, U.S. Dep't of Justice, Eli Lilly and Company Agrees to Pay $1.415 Billion To Resolve Allegations of Off-Label Promotion of Zyprexa (Jan. 15, 2009), *available at* http://www.justice.gov/opa/pr/2009/January/09-civ-038.html. Zyprexa was approved for use with certain psychotic disorders such as Bipolar I Disorder and schizophrenia. Eli Lilly marketed it to primary care physicians in nursing homes and assisted living facilities for unapproved uses such as treating dementia, Alzheimer's dementia, depression, anxiety, and sleep problems, as well as behavioral symptoms such as agitation, aggression, and hostility. The information also alleges that building on its unlawful promotion and success in the long-term care market, Eli Lilly executives decided to market Zyprexa to primary care physicians. In October 2000, Eli Lilly began an off-label marketing campaign targeting primary care physicians, even though the company knew that there was virtually no approved use for Zyprexa in the primary care market. Eli Lilly trained its primary care physician sales representatives to promote Zyprexa by focusing on symptoms, rather than Zyprexa's FDA-approved indications. *Id.*

9. Mina Kimes, *Bad to the Bone*, FORTUNE, Oct. 8, 2012, at 140.

10. *See* Henney, *supra* note 4, at 305; David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006).

11. *See infra* note 368 and accompanying text.

12. *See* John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 305–06 (2010).

13. *See id.*

prescription may be a medically sound option for many physicians, off-label promotion carries substantial risks. The following example illustrates some of those risks.

The FDA approved a medical "bone cement" for use in arm and skull surgeries.[14] The product, Norian XR, filled fractures and essentially became part of the bone.[15] The manufacturer of the product sought to use it in other types of surgeries, such as vertical compression fractures of the spine (VCFs).[16] Spurred on by the knowledge that Americans suffer some 500,000 VCFs a year, as well as research that indicated surgeons' interest in such a product, the company tested the product in various ways, including clinical trials that did not have the FDA's approval.[17] The FDA was concerned about use of the product in connection with spinal fractures because the bone cement could leak into the numerous arteries in the spine, causing severe and fatal clotting.[18] The label approved by the FDA on the product cautioned against use in surgeries for VCFs.[19]

Despite warnings from the FDA, Norian and its parent company, Synthes, made a calculated decision to promote the use of the product off-label for VCFs.[20] At least five people died of pulmonary clots shortly after the bone cement was injected during spine surgery.[21] One physician whose patient died on the operating table stated that the sales representative had pushed the product and that he was not clear about the product's status on the market.[22] His partner, however, believed the product was safe and effective, and continued to use it; he subsequently lost a patient during surgery.[23] Ultimately, use of the product for VCFs

14. Kimes, *supra* note 9, at 144.
15. *Id.* at 142.
16. *Id.* at 144.
17. *Id.*
18. Before the company began marketing the product for use in VCFs, tests showed that the bone cement caused blood clots when mixed with human blood. *See* Press Release, U.S. Dep't of Justice, Former Executives of International Medical Device Maker Sentenced to Prison in Unlawful Clinical Trials Case (Nov. 21, 2011), *available at* http://www.fda.gov/ICECI/CriminalInvestigations/ucm280937.htm. Tests of the product on pigs also showed that clots formed in the lungs. *Id.*
19. Kimes, *supra* note 9, at 144–45.
20. *Id.* at 144.
21. *Id.* at 142.
22. *Id.* at 150.
23. *Id.*

was halted.[24] Both Synthes and Norian pled guilty to numerous misdemeanors and paid substantial fines.[25] Four executives were charged as "responsible corporate officers."[26] They pled guilty to one misdemeanor count of shipping adulterated and misbranded Norian XR in interstate commerce and were sentenced to several months in jail.[27]

The outrageous facts of this case demonstrate the extreme harm that can result from off-label promotion of drugs.[28] But the case illustrates several points that are critical to the debate about off-label promotion even in cases that are less tragic. First, the company was willing to overlook serious risks associated with its product to reach a large, lucrative market.[29] Second, the case demonstrates the misconception that because a drug is approved for one use, it must be safe for other uses.[30] As the Norian case illustrates, a product can be safe and effective for some uses and excessively risky for others.[31] Third, the company chose to avoid the time-consuming and expensive FDA approval process to get its product to market quickly.[32] Fourth, surgeons were led to believe the product was safe and were not fully informed of the risks associated with the product.[33] Fifth, patients were unaware that they were the victims of experimentation.[34]

The case also demonstrates that courts are inaccurate in assuming that doctors, as "learned intermediaries," can successfully safeguard their patients from the aggressive marketing strategies of pharmaceutical

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24. *Id.* Not only did the company continue to market the product until after the third death it also failed to report details of the deaths to the FDA as required. *See* Press Release, U.S. Dep't of Justice, *supra* note 8.

25. *See* Press Release, U.S. Dep't of Justice, *supra* note 8.

26. *Id.*

27. *Id.*

28. The dangers associated with off-label promotion are numerous. For some examples of serious health issues associated with off-label promotion and use, see Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 226 (2011), which details individual patient risks and the risks to the health care system.

29. *See* Kimes, *supra* note 9, at 144.

30. *Id.* at 149.

31. *Id.* at 142.

32. FDA approval of medical devices is governed by the FDCA as amended by the MDA. *See* 21 U.S.C. §§ 351–360n-1 (2012). Although some devices require a premarket approval application before they may be marketed to the public, a manufacturer may seek an Investigational Device Exemption (IDE) to conduct tests on human subjects without premarket approval. *See id.* § 360j(g). The IDE is designed to "encourage . . . the discovery and development of useful devices . . . [and] to maintain optimum freedom for scientific investigators." *Id.* The manufacturer of Norian, however, opted not to seek an IDE. *See* Kimes, *supra* note 9, at 146.

33. *Id.* at 149.

34. *Id.* at 142.

companies.[35] The medical literature is replete with information about the impact that pharmaceutical companies have on doctors' decisions and prescribing habits and the inability of doctors to discern truthful from false or misleading information.[36]

In response to an increase in government prosecution of cases involving off-label promotion, the industry has complained that such prosecutions are overly aggressive.[37] It is more likely, however, that the government has responded appropriately to increasingly aggressive marketing strategies that put patients at risk. The off-label promotion of Neurontin provides an example of the calculated and extensive marketing strategies a company might employ.[38] Approved for use in conjunction with other drugs to

35. *See* discussion *infra* Part IV.B.

36. *See* discussion *infra* Part IV.B.

37. *See* Osborn, *supra* note 13, at 301 (describing the American pharmaceutical industry as "under siege" and referring to government investigations as "intrusive"). For a list of cases settled between 2004 and 2011 involving off-label promotion by pharmaceutical companies, see *List of Off-Label Promotion Pharmaceutical Settlements*, WIKIPEDIA, http://en.wikipedia.org/wiki/List_of_off-label_promotion_pharmaceutical_settlements (last modified Aug. 9, 2014). The healthcare advocacy group Public Citizen reported that between November 2, 2010, and July 18, 2012, there were seventy-four civil and criminal judgments and settlements against pharmaceutical companies, totaling $10.2 billion. SAMMY ALMASHAT & SIDNEY WOLFE, PUBLIC CITIZEN, PHARMACEUTICAL INDUSTRY CRIMINAL AND CIVIL PENALTIES: AN UPDATE 4 (2012), *available at* http://www.citizen.org/documents/20731.pdf. Not all of the settlements involved unlawful promotion, although seven of the top ten did. *See* Eric Palmer, *10 Largest Settlements and Judgments*, FIERCEPHARMA (Oct. 17, 2012), http://www.fiercepharma.com/story/10-largest-settlements-and-judgments/2012-10-17; *see also* Erika Kelton, *Off-Label Pharma Prosecutions Won't Be Silenced by First Amendment Decision*, FORBES (Jan. 4, 2013, 1:10 PM), http://www.forbes.com/sites/erikakelton/2013/01/04/off-label-pharma-prosecutions-wont-be-silenced-by-first-amendment-decision/ (urging the U.S. Department of Justice to continue prosecutions of off-label marketing after a U.S. court of appeals found a particular prosecution violated free speech rights).

38. *See* United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 45 (D. Mass. 2001). Pfizer acquired Warner Lambert, including its pharmaceutical division, Parke-Davis, in 2000. *2000: Pfizer Joins Forces with Warner-Lambert*, PFIZER.COM, http://www.pfizer.com/about/history/pfizer_warner_lambert (last visited Aug. 25, 2014). Pfizer maintains that the activity in question took place before its acquisition. *See* Stephanie Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN ST. L. REV. 41, 58 n.93 (2005). Each of the companies was named as a defendant in the suit. *Id.* For a more detailed description of the issues involved in the case, see generally *id.* at 58–64. Pfizer paid $430 million to settle the suit brought by the U.S. Department of Justice. *Id.* at 64. In subsequent litigation, Kaiser Foundation Health Plan and Kaiser Foundation Hospitals sued Pfizer, claiming that the off-label promotion of Neurontin caused them to purchase Neurontin for off-label indications such

treat epilepsy and for dosages ranging between 900 to 1800 milligrams per day, Parke-Davis marketed the drug for off-label uses including bipolar disorder, pain, and migraines, and for dosages exceeding 4800 milligrams per day, without any proof that the drug was safe or effective for these indications.[39] Internal company documents revealed that one employee referred to Neurontin as "the 'snake oil' of the twentieth century."[40] The off-label marketing effort was referred to in Parke-Davis memoranda as a "strategic swerve" to increase profits from Neurontin.[41] Pfizer's off-label promotion of Neurontin included delaying the publication of studies that indicated there was no evidence of Neurontin's efficacy for the off-label uses and suppressing, spinning, or neutralizing negative studies.[42] The company also engaged in a "publication strategy" to promote the drug and hired doctors to talk about off-label uses.[43] One of the key components of the marketing strategy was to have sales representatives, or detailers, promote Neurontin's off-label uses directly to physicians.[44] Taped voicemail messages indicated the scope of the company's deliberate attempt to promote off-label uses, without regard for the public's health and safety. One senior executive, explaining the "Neurontin push," rallied his sales representatives with the following speech:

> I want you out there every day selling Neurontin . . . holding their hand, whispering in their ear—Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything . . . . I don't want to see a single patient

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as migraines and bipolar disorder. *See* Greg Stohr, *Pfizer Rejected by Top Court on Neurontin Marketing Suits*, BLOOMBERG (Dec. 9, 2013, 4:19 PM), http://www.bloomberg.com/news/2013-12-09/pfizer-rejected-by-top-court-on-neurontin-marketing-suits.html. After a five-week jury trial, the jury found that Pfizer violated the Racketeer Influenced and Corrupt Organizations Act (RICO) with respect to its promotion of Neurontin for off-label uses of bipolar disorder, migraine, neuropathic pain, and dosages exceeding 1800 milligrams a day. *See In re* Neurontin Mktg. & Sales Practices Litig. v. Pfizer, Inc., No. 04-cv-10739-PBS, 2011 WL 3852254, at *1 (D. Mass. Aug. 31, 2011). The jury awarded damages of $47 million to Kaiser, which the court trebled pursuant to RICO. *Id.* Pfizer appealed the verdict on a causation issue, but the U.S. Court of Appeals for the First Circuit affirmed the judgment of the lower court. *See In re* Neurontin Mktg. & Sales Practices Litig. v. Pfizer, Inc., 712 F.3d 21, 46, 51 (1st Cir. 2013). Numerous cases against Pfizer for the off-label promotion of Neurontin are ongoing. *See, e.g.*, Owens v. Pfizer, Inc., No. 02-cv-01390-FSH-MAH (D.N.J.).

39. *See Parke-Davis*, 147 F. Supp. 2d at 48–49.

40. *In re Neurontin*, 2011 WL 3852254, at *8.

41. *Id.* at *6.

42. *See* Stephanie Saul, *Experts Conclude Pfizer Manipulated Studies*, N.Y. TIMES, Oct. 8, 2008, at B4, *available at* http://www.nytimes.com/2008/10/08/health/research/08drug.html.

43. *In re Neurontin*, 2011 WL 3852254, at *1.

44. *See id.* at *25.

> coming off Neurontin before they've been up to at least 4,800 milligrams a day.[45]

The Neurontin marketing strategy demonstrates that companies can infiltrate the marketplace with misleading information on numerous fronts. Moreover, the Neurontin example shows that such marketing strategies pay off, perhaps even after paying fines for violating the law. Lifetime sales for Neurontin, if marketed as approved by the FDA, were projected to be approximately $500 million.[46] Following the company's off-label marketing strategy, which began in 1995, projections indicate that ninety percent of Neurontin prescriptions were for off-label uses and sales soared from $97.5 million in 1995 to approximately $2.7 billion in 2003.[47]

Pharmaceutical companies maintain that most cases involving off-label promotion settle because the risk of being excluded from participation in federal and state healthcare programs is too great.[48] Recently, however, several defendants have asserted that off-label promotion is speech protected by the First Amendment.[49] Two cases in

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45. *Drug Giant Accused of False Claims*, NBC NEWS (July 11, 2003), http://nbcnews.com/id/3079883/ns/dateline_nbc/drug-giant-accused-false-claims (transcribing a July 11, 2003 *Dateline* interview with David Franklin, a former Warner-Lambert senior executive).

46. *In re Neurontin*, 2011 WL 3852254, at *6.

47. Julie Schmit, *Drugmaker Admitted Fraud, But Sales Flourish*, USA TODAY (Aug. 16, 2004, 11:14 PM), http://usatoday30.usatoday.com/money/industries/health/drugs/2004-08-16-neurontin-cover_x.htm.

48. *See* Katherine A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 180 (2007) ("Companies are unwilling to take the risks associated with going to trial, including the risk of exclusion from participation in federal and state healthcare programs."). Under 42 U.S.C. section 1320a-7, individuals and entities may be excluded from participating in Medicare and State healthcare programs if convicted of healthcare fraud. 42 U.S.C. § 1320a-7(a)(3) (2012).

49. In 2011, Par Pharmaceutical, Inc. filed a complaint seeking a declaratory judgment that the First Amendment prohibits FDA regulations that criminalize off-label promotion of FDA-approved drugs. *See* Par Pharmaceutical, Inc. v. United States, No. 11-cv-01820 (Oct. 14, 2011). The complaint maintained that the regulations criminalize manufacturers' speech even if it is truthful and non-misleading. *Id.* at 2. Par Pharmaceutical's product, Megace ES, is FDA-approved for the treatment of anorexia, cachexia, or unexplained, significant weight loss in patients diagnosed with AIDS. *Id.* at 13–14. According to Par Pharmaceutical, the company sought to provide truthful information about the on-label use of Megace to doctors who might prescribe for off-label uses in treating wasting in cancer and geriatric patients. *Id.* at 22–26. The company stated that a "manufacturer cannot be deemed to intend an off-label use merely because the

which the defendants asserted a First Amendment defense have reached the U.S. courts of appeals. In *United States v. Caronia*, the U.S. Court of Appeals for the Second Circuit held in a 2-1 decision that provisions of the Food, Drug, and Cosmetic Act (FDCA) cannot be interpreted to prohibit truthful, off-label promotion.[50] In *United States v. Harkonen*, the U.S. Court of Appeals for the Ninth Circuit, in an unpublished per curiam decision, held that the First Amendment does not protect fraudulent off-label speech.[51] The cases are not incompatible. The *Harkonen* decision focuses narrowly on the fraudulent nature of the off-label promotion and the defendant's intent to defraud, whereas the *Caronia* case focuses more broadly on off-label promotion as protected speech.[52]

The pharmaceutical industry's challenges in *Harkonen* and *Caronia* are the latest of several attempts to loosen the FDA's control over various marketing strategies. In previous cases, the industry succeeded in weakening FDA restrictions on dissemination of off-label promotion in printed materials and of material presented at continuing medical education events (CMEs).[53] The industry has increasingly sought First Amendment protection for the speech of pharmaceutical representatives who promote drugs for off-label uses to doctors through detailing.[54] *Detailing*, the type of promotion at issue in *Caronia*, involves promoting drugs and devices to doctors in their offices.[55] Detailing is especially important to off-label promotion because there is no prohibition against

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manufacturer sells a drug with knowledge that physicians will prescribe the drug for an off-label use." *Id.* at 32; *see also* Thomas Sullivan, *Par Pharmaceuticals vs. FDA Calling for Truthful Speech vs. FDA Approved*, POL'Y & MED. (Oct. 18, 2011), http://www.policymed.com/2011/10/phar-pharmaceuticals-vs-fda-calling-for-truthful-speech-vs-fda-approved.html (discussing the case). Par Pharmaceutical dropped the suit as part of a settlement in which it agreed to plead guilty to a misdemeanor charge for misbranding the drug and pay criminal and civil fines. *See* Kristin Jones, *Par Pharmaceutical To Settle Off-Label Charges*, WALL ST. J. (Mar. 5, 2013, 2:26 PM), http://online.wsj.com/news/articles/SB10001424127887324178904578342492178241564. Allergan, the manufacturer of Botox, also challenged FDA restrictions on off-label promotion on First Amendment grounds. *See* Natasha Singer, *Botox Maker's Suit Cites Free Speech*, N.Y. TIMES, Oct. 3, 2009, at B3, *available at* http://www.nytimes.com/2009/10/03/business/ media/03drug.html?_r=0. Allergan dropped its suit as part of its settlement with the government. Press Release, U.S. Dep't of Justice, Allergan Agrees To Plead Guilty and Pay $600 Million To Resolve Allegations of Off-Label Promotion of Botox, No. 10-988 (Sept. 1, 2010), *available at* http://www.justice.gov/opa/pr/2010/september/10-civ-988.html.

50. 703 F.3d 149, 168 (2d Cir. 2012).

51. 510 F. App'x 633, 636 (9th Cir. 2013) (per curiam).

52. *See Caronia*, 703 F.3d at 168; *Harkonen*, 510 F. App'x 633 at 638.

53. *See* discussion *infra* Part II.C.1.

54. *See supra* note 49 and accompanying text.

55. *See* Allison Torres Burtka, *Court Strikes Down Law Protecting Doctors' Prescription Data*, TRIAL, July 2007, at 84, 84.

doctors prescribing FDA-approved drugs for off-label uses and it has proven to be one of the most impactful ways of changing doctors' prescribing habits.[56]

The argument that off-label promotion is protected by the First Amendment received a boost from two U.S. Supreme Court decisions that addressed advertising and marketing in the pharmaceutical context. In 2002, in *Thompson v. Western States Medical Center*, the Court held that a law prohibiting pharmacies from advertising that they compounded specific drugs violated the First Amendment.[57] In 2011, the Court held in *Sorrell v. IMS Health Inc.* that a Vermont statute prohibiting pharmaceutical companies from using prescriber-identifying information for marketing purposes violated the First Amendment.[58] Language in these decisions provided ammunition for challenging restrictions on off-label promotion by detailers.[59] This Article questions the reach of the U.S. Supreme Court's decisions in *Western States* and *IMS Health*, and whether the Second Circuit's reliance on these cases in *Caronia* is misplaced.

Part II of this Article explains the laws and regulations that limit off-label promotion as well as exceptions and safe harbors for off-label promotion and dissemination of information. It also summarizes cases that paved the way for the First Amendment challenge in *Caronia*. Part III details the U.S. Court of Appeals for the Second Circuit's reasoning in *Caronia* and its reliance on the U.S. Supreme Court's decisions in *Western States* and *IMS Health.* The dissenting opinion in *Caronia*, which raises important arguments against the majority's reasoning, is summarized. In Part IV, an examination of the relationship between pharmaceutical representatives and physicians reveals that courts should not assume that off-label promotion provides valuable information or that doctors are able to distinguish between misleading and nonmisleading information. In Part V, the Article summarizes the Ninth Circuit's decision in *Harkonen*. The case demonstrates that the government may have more success focusing on the false or misleading nature of off-label promotion rather than the more technical charge of misbranding. Nevertheless, *Caronia* does not signal a significant change in how the

56. *See* discussion *infra* Part IV.B.
57. 535 U.S. 357, 377 (2002).
58. 131 S. Ct. 2653, 2672 (2011).
59. *See infra* Part III.B.

government will view off-label promotion. The errors in the prosecution of Caronia can be easily rectified. Moreover, contrary to the decision in *Caronia*, courts should recognize that regulations prohibiting off-label promotion withstand constitutional scrutiny. This Article argues that off-label promotion is more appropriately characterized as speech that does not deserve First Amendment protection because it is inherently misleading. Furthermore, even if restrictions of off-label promotion are subjected to First Amendment analysis, the heightened scrutiny standard used in *IMS Health* does not apply and the restrictions easily survive *Central Hudson* analysis.[60] The Article concludes that the government should not be deterred from prosecuting companies and sales representatives who promote drugs for off-label uses or by the industry's attempt to use the First Amendment as a shield to protect itself from fraudulent and deceptive marketing techniques.

II. THE PARAMETERS OF OFF-LABEL PROMOTION: RULES, REGULATIONS, AND COURT DECISIONS

Regulations related to prohibiting off-label promotion of drugs require a balancing of important goals: ensuring that the medical community has timely and accurate information about new advances in science and protecting the public health through the FDA's premarket approval process. Rules and regulations, as well as interpretations by courts, should seek to encourage the exchange of scientific information while maintaining a check on promotional information that is more likely to mislead than to inform. The following subparts provide background information for understanding the First Amendment challenges to off-label promotion.

A. What Is Off-Label Promotion?

Since 1962, the FDCA has required premarket approval of drugs for each indicated use before distribution in interstate commerce.[61] The FDA evaluates whether a drug is safe and effective under the conditions in the proposed labeling and ensures that the labeling is not "false or misleading in any particular."[62] If a company discovers new uses for a drug, new populations to treat, or new dosages, such uses must be approved by the FDA; otherwise, they are considered to be off-label.[63]

60. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980).

61. *See* 21 U.S.C. §§ 331(d), 355(a) (2012). For a history of FDA regulation in the drug industry, see Helm, *supra* note 48, at 124–46.

62. 21 U.S.C. § 355(d) (2012).

63. *See* 21 U.S.C. § 321(p) (2012).

Because the FDA approval process is time-consuming and expensive, drug manufacturers may seek to bypass the approval process by marketing the drug off-label.[64] Such promotion may be a tempting option if a company seeks to maximize a drug's potential by reaching a larger, more lucrative market before the patent expires or to avoid the time, costs, and risks associated with the trials required for FDA approval. For example, the government alleged that GlaxoSmithKline promoted its antidepressant drug Paxil off-label because it promoted the drug to a population that was not approved by the FDA.[65] The FDA-approved label for Paxil contained a black box warning, stating that antidepressants may increase the risk of suicidal thinking in patients under eighteen.[66] The government alleged that the company prepared and distributed misleading articles about the efficacy of the drug for the under-eighteen population and failed to make available data from trials that showed such use was not effective.[67] By seeking to introduce a product to an unapproved population and by providing information that was contrary to the FDA-approved label, a company would be guilty of misbranding.[68] GlaxoSmithKline settled the lawsuit.[69]

Although neither the FDCA nor FDA regulations specifically prohibit off-label promotion, a combination of provisions and regulations indicates that promoting off-label necessarily leads to illegal activity. The FDCA

64. A New Drug Application to the FDA requires detailed reports of preclinical and clinical trials demonstrating safety and efficacy and the proposed labeling for the drug. 21 U.S.C. § 355(b) (2012). The requirements for an Investigational New Drug Application are set forth at 21 C.F.R. § 312.20 (2013). The various phases of an investigation, including initial volunteer studies, controlled clinical studies involving several hundred patients, and expanded and uncontrolled trials involving several hundred to several thousands of patients, are described in 21 C.F.R. § 312.21 (2013); *see also* Julie C. Relihan, Note, *Expediting FDA Approval of AIDS Drugs: An International Approach*, 13 B.U. INT'L L.J. 229, 233–49 (1995) (describing the drug approval process); *How Drugs Are Developed and Approved*, FDA, http://www.fda.gov/drugs/development approvalprocess/howdrugsaredevelopedandapproved (last updated Feb. 13, 2014) (describing the same).

65. Press Release, U.S. Dep't of Justice, GlaxoSmithKline To Plead Guilty and Pay $3 Billion To Resolve Fraud Allegations and Failure To Report Safety Data (July 2, 2012), *available at* http://www.justice.gov/opa/pr/2012/July/12-civ-842.html.

66. *Id.*

67. *Id.*

68. *Id.*

69. *Id.* The company also pleaded guilty to misbranding charges related to its drug Wellbutrin, which was approved for Major Depressive Disorder but marketed off-label for weight loss, sexual dysfunction, and Attention Deficit Hyperactivity Disorder. *Id.*

prohibits introducing a drug into commerce without proper labeling about its indicated use, a practice referred to as misbranding.[70] Because labeling requirements are construed in a very broad manner, including oral representations made by pharmaceutical representatives, a representative who gives information about off-label use to a doctor with the intent that the drug be distributed in commerce is misbranding the drug.[71]

Marketing for pharmaceutical products and devices may include information provided in printed materials and advertisements, but it is often done through oral communication by sales representatives in a doctor's office, a practice referred to as detailing.[72] Doctors are a critical link in the effort to introduce an off-label use. Because the FDA does not interfere with the practice of medicine, doctors may prescribe FDA-approved drugs for any use.[73] Thus, the restrictions that apply to pharmaceutical companies regarding off-label promotion do not limit a doctor's ability to prescribe drugs for off-label use. Convincing a doctor to prescribe drugs for off-label uses, then, is an effective route to new markets without FDA approval. One argument that the industry has used in support of off-label promotion is that speech that supports a lawful activity—off-label prescription and use—should not be restricted.[74] The government maintains, however, that allowing companies to promote uses that are not FDA-approved strikes at the very heart of the FDA's premarket approval system and jeopardizes the public health.[75] The following subparts summarize the rules and regulations, as well as the case law, relevant to off-label promotion.

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70. A drug is "misbranded" if the manufacturer alters the FDA-approved labeling to include any false or misleading statement. *See* 21 U.S.C. § 352(a) (2012).

71. *See* 21 C.F.R. § 201.128 (2014) (stating that "intended uses" refers to the "objective intent of the persons legally responsible for the labeling of drugs" and objective intent may be shown "by labeling claims, advertising matter, or oral or written statements by such persons or their representatives"); 21 U.S.C. § 352(f) (2012) (stating that a drug is misbranded if it does not include adequate directions for use).

72. *The Pharma Marketing Glossary*, PHARMA MARKETING NETWORK, http://www.glossary.pharma-mkting.com/detailing.htm (last visited Aug. 25, 2014).

73. 21 U.S.C. § 396 (2012) (providing that the FDA does not "limit or interfere with the authority of a health care practitioner to prescribe" approved drugs or devices "for any condition or disease"). The Physicians' Desk Reference states, "[o]nce a product has been approved for marketing, a physician may choose to prescribe it for uses, treatment regimens, or patient populations that are not included in approved labeling." PHYSICIANS' DESK REFERENCE, Foreword (67th ed. 2013). The U.S. Supreme Court has recognized that off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate." Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

74. *See infra* Part III.B.

75. *See* United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012).

B. Rules, Regulations, and Guidance on Information About Off-Label Promotion

Under the FDCA, pharmaceutical manufacturers may not introduce a new drug into interstate commerce unless the drug and its label have secured FDA approval.[76] The Act also prohibits the "introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded."[77] A drug is considered misbranded if its label contains misleading information, lacks information that is sufficient to support its safe use for approved indications, or includes information about unapproved uses.[78] A prohibition on the misbranding of drugs predates the modern FDA. In 1906, the Department of Agriculture's Bureau of Chemistry regulated drugs under the Pure Food and Drug Act, which prohibited interstate commerce in "adulterated" or "misbranded" drugs.[79]

The definitions of "labeling" and "intended use" further explain how misbranding charges are related to off-label promotion. The FDCA and FDA regulations make it clear that labeling includes any printed or oral statement, including oral statements made by pharmaceutical representatives.[80] Thus, when pharmaceutical sales representatives promote a drug for off-label use, it is clear that the information they provide is considered labeling. The intended use of a drug is determined by considering the "objective intent of the persons legally responsible for the labeling of drugs" as evidenced by the "labeling claims, advertising matter, or oral or written statements by such persons or their representatives."[81] Thus, when a pharmaceutical representative visits doctors in their offices and provides information about off-label uses, it is logical to conclude that the representative's intent is to introduce a misbranded drug into commerce. The information provided is labeling that has not been approved for the intended off-label use. Even though

76. 21 U.S.C. § 355(a) (2012).
77. 21 U.S.C. § 331(a) (2012).
78. *See* 21 U.S.C. § 352(f) (2012); 21 C.F.R. § 201.50 (2013).
79. Helm, *supra* note 48, at 125. The Pure Food and Drugs Act, ch. 3915, §§ 1–13, 34 Stat. 768, 768–72 (1906) was repealed in 1938.
80. *See* 21 U.S.C. § 321(k), (m) (2012); 21 C.F.R. § 202.1 (2013) (listing the regulations that govern prescription drug advertising). In *Kordel v. United States*, the Court held that a manufacturer may be found guilty of misbranding even though the product and the labeling information were shipped separately. 335 U.S. 345, 350 (1948).
81. *See* 21 C.F.R. § 201.128 (2013).

the doctor's off-label prescription is legal, the pharmaceutical company and its representatives may be prosecuted for misbranding.[82] Pharmaceutical manufacturers and their representatives can face misdemeanor charges for misbranding or felony charges for fraudulent misbranding.[83]

Although manufacturers are prohibited from introducing misbranded drugs into interstate commerce, the FDA has indicated that responding to unsolicited requests about off-label uses may not indicate intent to misbrand. In draft guidance published in 2011, the FDA issued nonbinding recommendations about how companies should respond to both private and public inquiries about off-label uses from health care professionals or consumers.[84] The FDA's recommendations respond to the growth of Internet and social media tools that enable interested parties to seek information about emerging medical treatments.[85] When consumers contact a company privately about off-label information, the company should respond privately with "truthful, non-misleading, accurate, and balanced" scientific information.[86] Responses should come from the company's medical affairs office, not its sales force, and should be narrowly tailored to the inquiry.[87] Responses should also include a copy of the FDA-approved labeling with a notice that the off-label use has not been approved by the FDA.[88] When inquiries are posted on a public forum, the draft guidance recommends that a firm should respond in a nonpromotional manner with contact information only about its own product.[89] The FDA states that if firms follow its suggested recommendations, it will not "use such responses as evidence of the firm's intent that the product be used for an unapproved or uncleared use."[90]

In addition to responding to unsolicited inquiries, the FDA has recognized that pharmaceutical manufacturers may disseminate certain printed material pertaining to off-label drug uses. In 2009, the agency issued nonbinding recommendations about the dissemination of off-label information in

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82. *See* Hyman, Phelps & McNamara P.C., *A Deep Dive into the Second Circuit's* Caronia *Decision, Potential Next Steps, and Potential Enforcement Fallout*, FDA L. BLOG (Dec. 12, 2012, 1:37 AM), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/12/a-deep-dive-into-the-second-circuits-caronia-decision-potential-next-steps-and-potential-enforcement.html.

83. *See* 21 U.S.C. § 333(a) (2012).

84. FDA, DRAFT GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES (2011) [hereinafter FDA, 2011 DRAFT GUIDANCE].

85. *Id.* at 3, 10.

86. *Id.* at 8.

87. *Id.* at 7, 9, 11.

88. *Id.* at 9.

89. *Id.* at 12.

90. *Id.* at 3.

scientific or medical journals (2009 FDA Guidance).[91] The agency stated that if the recommendations were followed, it would not consider dissemination of the materials to be evidence of the manufacturer's intent to introduce the product for an unapproved use.[92] The recommendations emphasize that materials be peer-reviewed, independent of manufacturer funding, and not significantly influenced by a financial relationship with the manufacturer.[93] The information should also be based on "scientifically sound" clinical investigations and not be false or misleading.[94] Recommendations also include that the materials be unabridged, accompanied by the approved labeling, and not attached to promotional materials.[95]

The recommendations on disseminating printed materials about off-label use are substantially less burdensome than previous regulations.[96] The FDA's revised thinking on this issue is largely due to successful

91. FDA, 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) [hereinafter FDA, 2009 GUIDANCE], *available at* http://www.fda.gov/oc/op/goodreprint.html. The regulations were revised in 2014. *See* Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices, 79 Fed. Reg. 11,793 (Mar. 3, 2014). For purposes of this paper, the information cited in the 2009 FDA Guidance is substantially similar. The 2014 FDA Draft Guidance recommends that dissemination of information about studies of unapproved uses meets the following conditions: the study was conducted by independent researchers; there is adequate substantiation for claims of safety and efficacy; and the study appears in a peer-reviewed journal. *Id.* at 11,794–95. The FDA's guidelines further suggest that the article be disseminated with the approved labeling; a comprehensive bibliography; publications that reach contrary results; and prominent disclosures of the drug's unapproved status, as well as potential conflicts of interest—including financial interests of the study's authors. *Id.*

92. FDA, 2009 GUIDANCE, *supra* note 91.

93. *Id.*

94. *Id.* Despite the FDA's new tolerance toward the dissemination of materials about off-label use, the misleading nature of some publications remains controversial. *See, e.g.*, Joanna K. Sax, *Protecting Scientific Integrity: The Commercial Speech Doctrine Applied to Industry Publications*, 37 AM. J.L. & MED. 203, 204–05 (2011) (explaining that some companies use publication tactics that promote misleading information and calling for a national registry of all clinical trials to increase transparency).

95. FDA, 2011 DRAFT GUIDANCE, *supra* note 84.

96. Washington Legal Found. v. Henney, 202 F.3d 331, 336 (D.C. Cir. 2000) (noting that, because of the change in regulations, the plaintiff no longer had a constitutional objection to the regulations).

litigation that challenged restrictions on First Amendment grounds.[97] This litigation is discussed in the following subpart.

C. The Road to Caronia

Through persistent efforts, the pharmaceutical industry has loosened FDA restrictions on off-label promotion. Challenges to restrictions on the dissemination of printed material about off-label uses were successful in the *Washington Legal Foundation* litigation.[98] The U.S. Supreme Court has not addressed off-label promotion through detailing, but the Court's cases expanding protection for commercial speech in general have provided fresh ammunition in the industry's battle for increased First Amendment protection.[99] In response to First Amendment challenges, the government has indicated that it may be more selective in deciding which cases to prosecute.[100] The following subpart summarizes cases that addressed First Amendment challenges to off-label promotion as well as the U.S. Supreme Court cases that had a substantial impact on the Second Circuit's holding in *United States v. Caronia*.[101]

1. The Washington Legal Foundation Cases: Dissemination of Printed Materials About Off-Label Use Is Protected by the First Amendment

In *Washington Legal Foundation v. Friedman*, the Washington Legal Foundation, a public interest law and policy center, challenged the constitutionality of several FDA policies and guidance documents (FDA Guidance) that sought to restrict manufacturers' distribution of journal

97. In *Washington Legal Foundation v. Friedman*, the court held that FDA guidance restricting certain forms of manufacturer promotion of off-label uses were unconstitutional restrictions of commercial speech under the First Amendment. 13 F. Supp. 2d 51, 74–75 (D.D.C. 1998), *vacated in part sub nom*. Washington Legal Found. v. Henney, 202 F.3d 331, 336-37 (D.C. Cir. 2000). *But see* Whitaker v. Thompson, 353 F.3d 947, 952–53 (D.C. Cir. 2004) (holding that the FDA did not violate the First Amendment's restrictions on commercial speech when it determined that a certain dietary supplement had to be approved as a drug before it could be marketed as effective in the treatment of a disease).

98. *Friedman*, 13 F. Supp. 2d at 69.

99. *See infra* Part III.B.

100. *See* Defendants' Memorandum in Support of Motion to Dismiss at 27, Par Pharmaceutical, Inc. v. United States, No. 1:11-cv-1820 (D.D.C. Jan. 11, 2012) ("While manufacturer speech is always a relevant factor in determining intended use, in the absence of other evidence that an unapproved use is intended, a drug manufacturer that engages in truthful and non-misleading speech about an approved use is not placing itself in violation of the FDCA.").

101. 703 F.3d 149 (2d Cir. 2012).

article reprints and textbooks to physicians if they contained information about off-label uses.[102] In general, the FDA Guidance stated that manufacturers should distribute only materials referencing off-label uses if the materials were unabridged and were primarily about approved FDA uses.[103] The FDA sought to "strike the proper balance between the need for an exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit companies from promoting products for unapproved uses."[104] The regulations pertained to so-called "enduring materials," which include journal articles and medical textbooks, and specifically targeted dissemination of such materials by pharmaceutical companies.[105] Among the requirements in the FDA Guidance, the Washington Legal Foundation objected most strenuously to the requirement that the primary focus of texts or reprinted articles distributed be about FDA-approved uses.[106]

The court analyzed the restrictions on disseminating printed materials about off-label use as commercial speech, finding that it met the criteria articulated by the U.S. Supreme Court in *Bolger v. Youngs Drug Products Corporation*[107]: the speech is concededly an advertisement; the speech refers to a specific product; and the speaker has an economic motive in disseminating the material.[108] Noting that the purpose of the commercial speech doctrine is to "protect consumers from misleading, deceptive or aggressive sales practices," the court stated that manufacturers have

102. 13 F. Supp. 2d at 54.

103. *Id.* at 58 (citing Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52,800 (Oct. 8, 1996) [hereinafter Reprint Guidance]).

104. *Id.* (quoting Reprint Guidance, *supra* note 103, at 52,800).

105. *Id.*

106. Brief for Appellee at 20–21, 24–26, Washington Legal Found. v. Henney, 202 F.3d 331, 336–37 (D.C. Cir. 2000) (No. 99-5304). Other requirements included that the reprint be from a peer-reviewed journal, prominent notification on the reprint of any differences from the approved labeling, and that the material not be false or misleading. *Washington Legal Found.*, 13 F. Supp. 2d at 58 (citing Reprint Guidance, *supra* note 103, at 52,801). The guidance also required that medical textbooks and compendia provide a balanced presentation and that the text not be substantially prepared or edited by the manufacturer. *Id.* (citing Reprint Guidance, *supra* note 103, at 52,801).

107. 463 U.S. 60, 66–67 (1983).

108. *Friedman*, 13 F. Supp. 2d at 64.

considerable financial resources to influence physicians and that they are more likely to disseminate only materials that favor their own product.[109]

Having concluded that the speech in question was properly classified as commercial, the court applied the test announced by the U.S. Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.[110] *Central Hudson*'s four-prong analysis considers: (1) whether the speech concerns lawful activity and is not misleading; (2) whether the government has a substantial interest in regulating; (3) whether the regulation materially advances the government's interest; and (4) whether the regulation is more extensive than necessary.[111] The court concluded that the FDA Guidance could not withstand constitutional scrutiny.[112] The *Friedman* court rejected the FDA's argument that off-label promotion is inherently misleading.[113] The court stated that the "FDA exaggerates its overall place in the universe" by suggesting that information about uses not approved by the FDA is inherently misleading.[114] In support of this conclusion, the court noted that the FDA did not object to physicians receiving the same information about off-label uses from sources other than the manufacturer.[115]

After concluding that off-label promotion is not inherently misleading, the court examined the three remaining factors under *Central Hudson*. The court found that the government had a substantial interest in regulating off-label promotion to protect the public health and in requiring manufacturers to seek approval for new uses.[116] It also found that these interests were materially advanced by the regulations because "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."[117] Nevertheless, the court found that the FDA Guidance was more restrictive of speech than necessary.[118] Full and unambiguous disclosure to physicians that the off-label uses are not FDA-approved would, according to the court, be a less burdensome and more effective manner of advancing the government's interests.[119] The court found that because less restrictive means of meeting its interest were

109. *Id.* at 65 (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 501 (1984)).
110. 447 U.S. 557 (1980).
111. *Id.* at 566.
112. *Friedman*, 13 F. Supp. 2d at 74.
113. *Id.* at 68.
114. *Id.* at 67.
115. *Id.*
116. *Id.* at 72.
117. *Id.*
118. *Id.* at 73.
119. *Id.*

available, the government failed to meet *Central Hudson*'s requirements and violated the First Amendment.[120] The court held that the FDA could not prohibit manufacturers from disseminating enduring materials "regardless of whether such [materials] include[] a significant or exclusive focus" on off-label uses because doing so unduly burdened speech.[121]

Some language in the decision, however, is critical to later First Amendment challenges to FDA restrictions. The court emphasized that its ruling covered a "*very* narrow form of manufacturer communication" and that the FDA could prohibit many other types of communication to physicians about off-label uses, including "person-to-person contact with a physician."[122] The court stated that these "incentives . . . to get off-label treatments on-label" were "central" to its decision, and that if manufacturers were "permitted to engage in *all* forms of marketing of off-label treatments, a different result might be compelled."[123]

Subsequent to the *Friedman* case, Congress passed the Food and Drug Administration and Modernization Act (FDAMA), which contained provisions about the dissemination of material about off-label use by manufacturers.[124] Section 401 of FDAMA was intended to supersede the previous FDA Guidance that was challenged in the *Friedman* case. Section 401 required manufacturers to submit a supplemental application to the FDA seeking approval of the off-label use within thirty-six months of dissemination of the material in question, provide the materials to the FDA sixty days prior to dissemination, disseminate materials in unabridged form, and disclose to recipients that the materials pertain to an unapproved use of the drug.[125] In *Washington Legal Foundation v. Henney*, the court held that the provisions of FDAMA, like the FDA Guidance provisions it had previously analyzed, were unconstitutional and infringed on manufacturers' First Amendment rights.[126] The court was particularly concerned about the requirements for supplemental applications, stating

120. *Id.* at 73–74.

121. *Id.* at 74. The court also held that the FDA could not prohibit manufacturers from suggesting content to Continuing Medical Education providers. *Id.* at 74–75.

122. *Id.* at 73.

123. *Id.*

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

125. Shane M. Ward, *WLF and the Two Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet*, 56 FOOD & DRUG L.J. 41, 47–48 (2001).

126. *See* Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999).

"[t]he supplemental application requirement of the act amounts to a kind of constitutional blackmail—comply with the statute or sacrifice your First Amendment rights."[127]

On appeal, the FDA maintained that the provisions of section 401 of FDAMA merely provided a "safe harbor" and that FDAMA did not authorize the FDA to prohibit or sanction speech.[128] The FDA's position led the U.S. Court of Appeals for the District of Columbia to declare the issue moot and to vacate the injunction of the lower court.[129] The result of the litigation was that manufacturers were free to disseminate reliable scientific information about off-label uses. In 2009, the FDA issued nonbinding recommendations about disseminating printed materials with information about off-label use; these guidelines were revised in 2014.[130]

2. Thompson v. Western States Medical Center*: Dissemination of Information About the Compounding of Specific Drugs Is Speech Protected by the First Amendment*

First Amendment challenges to the dissemination of information about certain drugs reached the U.S. Supreme Court in 2002. In *Thompson v. Western States Medical Center*, the drug compounding industry complained that certain provisions of FDAMA unconstitutionally burdened protected speech.[131] The Supreme Court's analysis in *Western States* was similar to that in the *Washington Legal Foundation* cases. The Court held that the restrictions on advertising or promoting compounded drugs violated the First Amendment's free speech guarantee.[132] Using the commercial speech analysis from its *Central Hudson* decision, the Court recognized that the restrictions advanced substantial government interests, but found that they were not narrowly tailored, as the test requires.[133]

Drug compounding is a process that is designed to tailor medication to the needs of an individual patient.[134] Because the FDA approval process would be prohibitively expensive and burdensome for such customized drugs, the FDA has left regulation of compounding primarily to the states and has not required compounders to seek approval for such

127. *Id.*
128. *See* Washington Legal Found. v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000).
129. *Id.* at 335–37.
130. *See supra* text accompanying notes 91–97.
131. 535 U.S. 357, 360 (2002).
132. *See id.* at 377.
133. *See id.* at 369–73. *See supra* text accompanying notes 110–111 (describing the *Central Hudson* test).
134. *Western States*, 535 U.S. at 360–61. The Court noted that compounding is a "traditional component of the practice of pharmacy" and "is taught as part of the standard curriculum at most pharmacy schools." *Id.* at 361.

drugs.[135] Nevertheless, the FDA became concerned that compounding could provide a loophole for some pharmacists to manufacture and sell drugs "under the guise of compounding."[136] Moreover, the government maintained that advertising is "a fair proxy for actual or intended large-scale manufacturing."[137] In other words, according to the government, advertising should not be necessary for traditional compounding because such prescriptions respond to individual needs. Consequently, section 503A of FDAMA recognized that compounded drugs are exempt from the FDA drug approval process in general, but required compounders to refrain from certain activities associated with manufacturers such as soliciting business and advertising.[138] The regulations allowed compounders to advertise their services in general, but prohibited them from advertising the compounding of specific drugs.[139] Pharmacies that specialized in compounding drugs challenged these provisions.[140]

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135. *See id.* at 362. An outbreak of fungal meningitis in 2012 associated with a product distributed by the New England Compounding Center (NECC) drew national attention to the compounding industry. *See* Denise Grady, *Second Illness Is Infecting Those Struck By Meningitis*, N.Y. TIMES, Nov. 3, 2012, at A14; Press Release, Exec. Office of Health and Human Servs., Commonwealth of Massachusetts, Alert—New England Compounding Center Product Recall Information (undated), *available at* http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy/pharmacy-alert-necc.pdf. A steroid injectable product received by approximately 14,000 patients across nineteen states caused sixty-four deaths and over 750 cases of fungal meningitis in twenty states. *See* Grady, *supra*, at A14. In response to the crisis, Congress amended the FDCA by passing the Drug Quality and Security Act to ensure the safety of compounded drugs. Pub. L. No. 113-54, 127 Stat. 587 (codified as amended at 21 U.S.C. § 301–399f (2013)). The Act has two distinct provisions. The Compounding Quality Act creates a program that allows compounding manufacturers to voluntarily submit to FDA oversight similar to that of traditional pharmaceutical manufacturers. The second provision, the Drug Supply Chain Security Act, implements a tracking system requiring manufacturers to affix bar codes to products introduced into the supply chain. Professor Kevin Outterson describes the balance that the FDAMA restrictions on advertising sought to achieve between traditional compounding activities and drug manufacturing. *See* Kevin Outterson, *Regulating Compounding Pharmacies After NECC*, 367 N. ENG. J. MED. 1969 (2012). According to Outterson, "[i]t's possible that if the Supreme Court hadn't struck down Section 503A, the tragedy at NECC could have been averted." *Id.* at 1971.

136. *See Western States*, 535 U.S. at 362. The regulations state that pharmacies may "not advertise or promote the compounding of any particular drug, class of drug, or type of drug," but may "advertise and promote the compounding service." 21 U.S.C. § 353a (2012).

137. *Western States*, 535 U.S. at 370–71.

138. *See* 21 U.S.C. §353a(c).

139. *See id.*

140. *Western States*, 535 U.S. at 360.

In considering whether the provisions prohibiting solicitation and advertising of compounded drugs violated the First Amendment, the Court used the *Central Hudson* analysis for commercial speech.[141] The government maintained that the FDAMA regulations met the *Central Hudson* test because they served three substantial interests: preserving the integrity of the FDA's new drug approval process that protects the public health; allowing compounded drugs to be available to those patients who need them; and balancing these competing interests.[142] The government further asserted that the restrictions on promotion and advertising separate small-scale compounding, which responds to individual patient need, from large-scale drug manufacturing.[143] The Court concluded, however, that even assuming that the restrictions would materially advance the government's interests, the regulations did not satisfy the *Central Hudson* test because they were not narrowly tailored.[144] The Court suggested several less burdensome alternatives that would be nonspeech related.[145] In short, the Court found that there was insufficient

141. *See id.* at 367–68.

142. *See id.* at 368.

143. *Id.* at 370–71.

144. *Id.* at 371–72. Justice Breyer authored a vigorous dissent, joined by the Chief Justice, Justice Stevens, and Justice Ginsburg. *See id.* at 378–90 (Breyer, J., dissenting). Justice Breyer wrote that "the Court seriously undervalues the importance of the Government's interest in protecting the health and safety of the American public." *Id.* at 378–79. Unlike the majority of the Court, the dissenting justices recognized that a restriction on advertising particular compounded drugs was part of a "finely tuned balance" between the risks and benefits associated with compounded drug prescriptions. *Id.* at 380–81. The dissenting justices recognized that traditional compounding relies on a particular doctor making a determination for a particular patient, whereas advertising compounded drugs has nothing to do with an individualized need or medical determination. *See id.* at 381–82. Justice Breyer stated that the restrictions on advertising particular compounded drugs "try to assure that demand is generated doctor-to-patient-to-pharmacist, not pharmacist-to-advertisement-to-patient-to-doctor." *Id.* at 382. The dissent criticized the Court's argument that restricting advertising is paternalistic in fearing that doctors or patients might make "bad decisions if given truthful information." *Id.* at 386–87. According to the dissent, the government seeks to prevent "the adverse cumulative effects of multiple individual decisions" which could in the aggregate "undermine the safety testing system, thereby producing overall a net balance of harm." *Id.*

145. *See id.* at 372. The Court suggested that the FDA could rely on factors listed in its 1992 Compliance Policy Guide that distinguished between compounding and large-scale manufacturing. For example, the court pointed out that the FDA could "prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received," "prohibit pharmacists from offering compounded drugs products at wholesale to other state licensed persons or commercial entities for resale," or "limit the amount of compounded drugs . . . that a given pharmacist or pharmacy sells out of state." *Id.* (citations omitted).

evidence that the restrictions on advertising were "necessary" as opposed to "merely convenient" in promoting the government's interests.[146]

3. United States v. Caputo*: The First Amendment Does Not Apply if the Use Is Unlawful*

The *Washington Legal Foundation* decisions regarding dissemination of printed materials about off-label use and the U.S. Supreme Court's expansive protection of advertising in *Western States* encouraged further challenges to restrictions on off-label promotion. In *United States v. Caputo*, the U.S. Court of Appeals for the Seventh Circuit discussed, but did not decide, whether a seller of drugs or medical devices has a constitutional right to promote off-label uses.[147]

In *Caputo*, the defendants were convicted on several charges, including introducing a misbranded device into interstate commerce. The FDA approved a small sterilizer exclusively for use with stainless steel instruments. Recognizing that there was no market for the FDA-approved use, the defendants marketed a larger version of the device for use in sterilizing a variety of surgical instruments.[148] When brass instruments were sterilized in the larger machine, a residue remained that caused corneal decomposition and loss of vision to patients. The defendants argued that off-label marketing of the larger machine for use with different kinds of instruments was speech protected by the First Amendment.[149] Because off-label use is legal, the defendants maintained, off-label promotion cannot be restricted.[150]

The Seventh Circuit did not have to reach the First Amendment issue because it concluded selling the device was not lawful.[151] Had the facts raised the issue of a machine lawfully sold but promoted for an off-label use, however, the court noted that its decision might have been different.[152] The court stated, "if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals . . . doesn't it make a good deal of sense to allow speech by the device's manufacturer,

146. *Id.* at 373.
147. *See* 517 F.3d 935, 940 (7th Cir. 2008).
148. *See id.* at 937.
149. *See id.* at 938.
150. *See id.*
151. *Id.* at 940.
152. *See id.* at 939.

which after all will have the best information?"[153] The court stated that the U.S. Supreme Court's analysis in *Western States* indicated that prohibiting manufacturers from "alerting consumers to lawful off-label uses" is "unconstitutional in at least some applications" and that "drugs [and by implication medical devices] are not a special case for first-amendment analysis."[154]

The Seventh Circuit recognized, however, that there are dangers associated with off-label promotion. Notably, the court stated that the FDA could withhold approval of any use of a drug or device if it anticipated the manufacturer would promote other uses, thereby depriving the public of uses that the FDA excludes.[155] The court cautioned that "a court should hesitate before extending an [] historical reading of the Constitution in a way that injures the very audience that is supposed to benefit from free speech."[156] The court stated that it "[f]ortunately" did not have to decide whether manufacturers may promote off-label because there was enough evidence for a jury to conclude that the larger machine was not lawfully sold.[157] The machine, it found, was not a mere modification of an approved device but a new device altogether. Without lawful use, the court held, there is no need for First Amendment analysis.[158]

4. Sorrell v. IMS Health, Inc.*: The First Amendment Protects Speech in Aid of Pharmaceutical Marketing*

In deciding a 2011 case, the U.S. Supreme Court made a strong statement about protecting the speech of pharmaceutical manufacturers.[159] The case involved the Vermont Prescription Confidentiality Law, which prohibited pharmaceutical companies and similar entities from using prescriber-identifying information for marketing purposes.[160] Addressing a First Amendment challenge to the statute, the Court held that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."[161] Significantly, the Court found that such speech is subject to "heightened judicial

153. *Id.*
154. *Id.*
155. *See id.* at 940.
156. *Id.*
157. *See id.* at 940–41.
158. *See id.*
159. *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011).
160. *See id.* at 2659.
161. *See id.*

scrutiny" rather than the intermediate scrutiny applied to commercial speech under the *Central Hudson* analysis.[162]

Data miners and pharmaceutical manufacturers of brand name drugs challenged the Vermont law.[163] Pharmacies are required by law to collect and maintain detailed files about each prescription filled.[164] The pharmacies can sell these records, containing a doctor's name and address, along with the amount of the drug prescribed, to data miners who, in turn, may lease the information to pharmaceutical companies.[165] The information is valuable to companies in effectively targeting doctors who might be inclined to change their prescribing habits.[166] Influencing doctors' prescribing practices is largely achieved through detailing, the practice of pharmaceutical sales representatives visiting doctors in their offices with information about specific products.[167] The Vermont legislature had concluded that the information that pharmaceutical marketers provide to doctors is "incomplete and biased."[168] Moreover, the legislature found that despite the inadequacy of the information, doctors rely on it because they do not have time to research the constant advances in new drugs.[169] In addition to protecting medical privacy interests, the state maintained that its law sought to prevent companies from using this information to influence doctors to prescribe the newest, most expensive brand name drugs, thereby driving up health care costs and exposing patients to newer drugs whose side effects may not yet be fully known.[170]

The Court's approach to the First Amendment issue was significant. Rather than using the well-established analysis for commercial speech under *Central Hudson*, the Court found that "heightened scrutiny" was required because the Vermont statute set forth content and speaker based restrictions.[171] The Court found that the Vermont law disfavored speech

162. *See id.*
163. *See id.* at 2660.
164. *See id.*
165. *See id.*
166. *See id.* at 2661.
167. *See id.*
168. *See id.*
169. *See id.*
170. *Id.* at 2659–61.
171. *See id.* at 2663–64. Justice Breyer dissented, joined by Justices Ginsburg and Kagan. *See id.* at 2673–85 (Breyer, J., dissenting). The dissent maintained that the "heightened" standard of review was not required and that the statute met the First Amendment standard for regulating commercial speech under *Central Hudson*. *See id.* Justice Breyer was particularly concerned that applying a "'heightened' First Amendment

with a particular content—marketing—when expressed by certain disfavored speakers—pharmaceutical manufacturers.[172] Thus, the Court found that the law suffered from viewpoint discrimination because the Vermont legislature designed the law to prevent marketers from more effectively selling high cost brand-name drugs, rather than lower priced generic drugs favored by the state.[173] Heightened scrutiny is required, the Court stated, "whenever the government creates 'a regulation of speech because of disagreement with the message it conveys.'"[174]

Stating that "content-based" and "viewpoint discriminatory" laws are presumptively invalid, the Court further demonstrated that the law would meet the same fate under *Central Hudson*'s less demanding standard for commercial speech.[175] Under *Central Hudson*, the state has the burden of proving that it has substantial interests in regulating and that those interests are directly advanced by the law in question.[176] The Court found that the law did not advance Vermont's purported interests in protecting patient privacy and preventing influence on doctors' prescribing habits in a direct manner, as required.[177] The confidentiality of prescription decisions is not protected, the Court reasoned, because only marketers are barred from using such information; researchers, journalists, and others are not denied access to the information.[178] The Court also rejected the state's argument that the law interfered with the doctor-patient relationship by influencing prescribing decisions.[179] The Court concluded that the fact that doctors find such speech persuasive does not remove it from First Amendment protection.[180] As in *Western States*, the Court emphasized the fact that the government cannot suppress information out of fear that the public will misuse that information.[181] Furthermore, the Court noted that doctors, as the recipients of information through detailing, are "'sophisticated and experienced' consumers."[182] The Court noted that a

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standard of review whenever . . . a [regulatory] program burdens speech would transfer from legislatures to judges the primary power to weigh ends and to choose means, threatening to distort or undermine legitimate legislative objectives." *Id.* at 2675 (citing Glickman v. Wileman Bros. & Elliott, Inc., 521 U.S. 457, 476 (1997)).

172. *See id.* at 2663 (majority opinion).

173. *See id.* at 2663–64.

174. *Id.* at 2664 (quoting Ward v. Rock Against Racism, 491 U.S. 781, 791 (1989)).

175. *See id.* at 2667–72.

176. *See id.* at 2667–68 (citing Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980)).

177. *See id.* at 2670.

178. *See id.* at 2668.

179. *See id.* at 2670.

180. *Id.*

181. *Id.* at 2670–7l (citing Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002)).

182. *Id.* at 2671 (quoting Edenfield v. Fane, 507 U.S. 761, 775 (1993)).

state is free to put forth its own views on topics such as a preference for generic drugs, but that it may not burden the speech of others who wish to promote brand-name drugs.[183]

As the cases from *Washington Legal Foundation* to *IMS Health* illustrate, First Amendment challenges to off-label promotion were well-established before the *Caronia* case was heard in federal district court in 2008. The industry had gained a significant victory in changing the FDA's thinking on the dissemination of printed materials. Language in U.S. Supreme Court decisions such as *Western States* and *IMS Health* encouraged the industry to expand First Amendment protection for off-label promotion by sales representatives.[184] Neither of the Supreme Court cases, however, specifically addressed issues raised by off-label promotion through detailing.[185] Furthermore, lower courts that considered the implications of off-label promotion through detailing expressed reservations and caution.[186]

III. THE *CARONIA* CASE

The case against Alfred Caronia, a sales representative for Orphan Medical, arose in the context of a government investigation of the company for the unlawful marketing and promotion of Xyrem, a powerful central nervous system drug, classified by the federal government as a "date rape" drug.[187] Orphan, the manufacturer of the drug, agreed to pay $20 million in penalties and victim compensation to resolve parallel criminal and civil investigations.[188] The agreement included a guilty plea by Orphan to one count of felony misbranding of a drug product for off-label uses under the FDCA.[189] Peter Gleason, a psychiatrist who the government

183. *Id.*
184. *See infra* Part III.
185. *See supra* Parts II.C.2, II.C.4.
186. *See, e.g.*, In re Neurontin Mktg., Sales Practices & Products Liab. Litig., 618 F. Supp. 2d 96, 112 (D. Mass. 2009) (finding detailers had a duty to disclose side effects of off-label use but failed to do so).
187. Jazz Pharmaceuticals acquired Orphan Medical in 2005. The U.S. Department of Justice's investigation began in 2006, when a former sales representative filed a suit under the False Claims Act on behalf of the United States. *See* Press Release, U.S. Attorney's Office for the E. Dist. of N.Y., Jazz Pharmaceuticals, Inc. Agrees To Pay $20 Million To Resolve Criminal and Civil Allegations in "Off-Label" Marketing Investigation (July 13, 2007), *available at* www.justice.gov/usao/nye/pr/2007/2007jul13a.html.
188. *See id.*
189. *See id.*

alleged was paid tens of thousands of dollars to illegally promote Xyrem, also pled guilty to a misdemeanor to conspire with Orphan Medical.[190] Dr. Gleason was sentenced to one year probation and a $25 fine.[191] Alfred Caronia, however, chose to go to trial and to appeal his conviction on the grounds that promotion of the off-label uses was protected speech under the First Amendment.[192]

A. The District Court Found That Prohibitions on Off-Label Promotion Withstood Constitutional Scrutiny

Alfred Caronia, a sales representative of the company that manufactures Xyrem, was charged with knowingly and intentionally conspiring with others to misbrand the drug by promoting it for off-label uses.[193] Caronia argued that because doctors can lawfully prescribe FDA-approved drugs for any use, the government cannot restrict truthful, non-misleading promotion by a pharmaceutical manufacturer.[194]

The drug that Caronia allegedly misbranded, Xyrem, is a powerful sleep-inducing depressant that the FDA approved for two indications: cataplexy, a condition associated with narcolepsy, and excessive daytime sleepiness associated with narcolepsy.[195] The side effects of the drug are so serious, including seizures, coma, and death, that Xyrem's labeling contains a black box warning, the most serious warning the FDA issues.[196] Designated as a Schedule III Controlled Substance for medical use, Xyrem cannot be sold or distributed to anyone other than for a prescribed use.[197]

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190. *See* Harvey Silverglate, *A Doctor's Posthumous Vindication*, WALL ST. J. (Dec. 25, 2012, 5:24 PM), http://online.wsj.com/news/articles/SB10001424127887323981504578174973015235686; Press Release, U.S. Attorney's Office for the E. Dist. of N.Y., Psychiatrist Charged with Conspiracy To Illegally Market the Prescription Medication Xyrem, Also Known As "Ghb," for Unapproved Medical Uses on Behalf of Its Manufacturer (Apr. 5, 2006), *available at* www.justice.gov/usao/nye/pr/2006/2006apr05.html.

191. Silverglate, *supra* note 190. Silverglate wrote that the decision by the U.S. Court of Appeals for the Second Circuit vindicated Gleason when Caronia "won the point" that Gleason had argued that "[t]he First Amendment protects the right of physicians, drug manufacturers, sales representatives and anyone else who wishes to convey truthful, factual information about the beneficial uses of drugs in the relief of illness and pain." *Id.* Silverglate states that Gleason's career and finances were ruined by the suit and that Gleason ultimately took his own life as a result. *Id.*

192. *See* United States v. Caronia, 576 F. Supp. 2d 385, 390 (E.D.N.Y. 2008), rev'd 703 F.3d 149 (2d Cir. 2012).

193. *Id.* at 389.

194. *Id.* at 393.

195. *Id.* at 388–89.

196. *Id.* at 389.

197. *Id.*

The government charged Caronia with conspiring to misbrand the drug because he promoted it for unapproved uses such as insomnia, fibromyalgia, muscle disorders, and chronic pain.[198] Despite the serious risks associated with Xyrem, Caronia stated that it was "a very safe drug," with no contraindications.[199] It is worth noting that Caronia was under substantial pressure to sell the drug for off-label uses: representatives were required to meet an annual sales quota of 520 bottles of Xyrem in 2005, the year of the allegedly illegal off-label promotion; meeting sales targets had a substantial impact on salaries; and Caronia ranked near the bottom of the company's national sales force.[200]

In analyzing the First Amendment defense to the charge of misbranding, the district court concluded that the speech in question was commercial because it satisfied the test articulated by the U.S. Supreme Court in *Bolger v. Youngs Drug Products Corp.*: (1) the expression is an advertisement; (2) it refers to a specific product; and (3) the speaker has an economic motivation for speaking.[201] Having concluded that Caronia's promotion of the drug qualified as commercial speech, the court employed the *Central Hudson* test to assess its constitutionality.[202] *Central Hudson* requires: (1) that the speech is lawful and not misleading; (2) that the government demonstrate a substantial interest; (3) that the regulation directly advances that interest; and (4) that the restriction is not more extensive than necessary.[203]

The district court found that the FDCA's restrictions on off-label promotion were constitutional. The court recognized that the government has a substantial interest in the health and safety of its citizens as well as in subjecting drugs to the FDA premarket approval process.[204] The court found that restrictions on off-label promotion by manufacturers directly advance the FDA's interest in maintaining its approval process.[205] Citing *Friedman* and *Caputo*, the court recognized that manufacturers

198. *Id.*
199. United States v. Caronia, 703 F.3d 149, 172 n.3 (2d Cir. 2012) (Livingston, J., dissenting).
200. *See id.*
201. *Caronia*, 576 F. Supp. 2d at 396 (citing Bolger v. Youngs Drug Prods. Corp., 463 U.S. 60, 66–68 (1983)).
202. *See id.* at 396–402 (applying the test established in Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557 (1980)).
203. *See Central Hudson*, 447 U.S. at 564.
204. *See Caronia*, 576 F. Supp. 2d at 398.
205. *See id.*

have little incentive to seek FDA approval for off-label uses and that restricting marketing behavior is one of the few methods in which the FDA can encourage manufacturers to seek FDA approval for new uses of a drug that has been approved.[206]

Finally, the court found that the FDA restrictions on off-label promotion are not more restrictive than necessary.[207] Building on the cautionary language raised in *Friedman* and *Caputo*, the court concluded that the FDA's prohibition on off-label promotion is necessary "to ensure that manufacturers will not seek approval only for certain limited uses of drugs, then promote that same drug for off-label uses, effectively circumventing the FDA's new drug requirements."[208]

B. The Second Circuit Held That Restricting Off-Label Promotion by Pharmaceutical Representatives Violates the First Amendment

The U.S. Court of Appeals for the Second Circuit reversed the lower court's ruling, finding that prosecuting a pharmaceutical representative for promoting the lawful, off-label use of an FDA-approved drug violates the First Amendment.[209] In a 2-1 decision, the court stated that the government improperly construed the misbranding provision of the FDCA to prohibit promotional speech.[210]

The court noted that the FDCA criminalizes misbranding or conspiring to misbrand a drug, but the Act does not expressly prohibit the promotion of a drug for off-label use.[211] Although the government argued that it emphasized promotion only as evidence of intent to misbrand, the court was not persuaded.[212] Instead, the court found the trial record showed that the defendant was prosecuted and convicted for his speech.[213] Although jury instructions included explanations about the elements of misbranding and conspiring to misbrand, the court found that the government's summation, together with the jury instructions, gave the impression that the off-label promotion itself was prohibited.[214] According to the Second Circuit, construing the FDCA's misbranding provisions to

206. *See id.* (referencing United States v. Caputo, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) and Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *vacated in part sub nom*. Washington Legal Found. v. Henney, 202 F.3d 331, 336-37 (D.C. Cir. 2000)).
207. *See id.* at 401.
208. *Id.* (citing *Friedman*, 13 F. Supp. 2d at 72).
209. *See* United States v. Caronia, 703 F.3d 149, 168–69 (2d Cir. 2012).
210. *See id.*
211. *See id.* at 154.
212. *See id.* at 160–62.
213. *Id.* at 161.
214. *See id.*

criminalize the simple promotion of a drug's off-label use by pharmaceutical representatives would "run afoul of the First Amendment."[215]

When the Second Circuit heard the appeal in *United States v. Caronia*, it had the benefit of the U.S. Supreme Court's decision in *Sorrell v. IMS Health*,[216] which had not been decided when the district court reached its decision. The Court's statement in *IMS Health* that "speech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment" together with the "heightened scrutiny" standard the Court used changed the analysis of the *Caronia* case substantially.[217]

In *IMS Health*, the Court required heightened scrutiny because the statute imposed both content and speaker based restrictions, which the Court stated are "presumptively invalid."[218] In *Caronia*, the Second Circuit found that the FDCA's misbranding provisions impose similar restrictions. Off-label promotion is content-based, according to the court, because it distinguishes between favored speech—uses that are FDA-approved—and disfavored speech—uses that are not FDA-approved.[219] Prohibiting off-label promotion is speaker-based, the court reasoned, because it targets one kind of speaker—pharmaceutical manufacturers and their representatives—while allowing others, such as doctors and academics, to speak about off-label use.[220]

Following the Supreme Court's analysis in *IMS Health*, the Second Circuit also demonstrated that restrictions on off-label promotion could not withstand constitutional scrutiny under *Central Hudson*. The court recognized the government's substantial interests in reducing the public's exposure to unsafe and ineffective drugs and in preserving the FDA's drug approval process.[221] The court found, however, that a prohibition on off-label promotion failed to satisfy *Central Hudson*'s requirement that the law directly advance the government's interest because the

215. *Id.* at 162.
216. 131 S. Ct. 2653 (2011).
217. *Id.* at 2659, 2664 (providing the standards used by the U.S. Second Circuit Court of Appeals); *compare* United States v. Caronia, 576 F. Supp. 2d 385, 396–402 (E.D.N.Y. 2008) (decided prior to *IMS Health*), *with Caronia*, 703 F.3d at 163–64 (applying the standards set forth in *IMS Health*).
218. *IMS Health*, 131 S. Ct. at 2667 (citing R.A.V. v. City of St. Paul, 505 U.S. 377, 382 (1992)).
219. *See Caronia*, 703 F.3d at 165.
220. *See id.*
221. *See id.* at 166.

FDA's approval process anticipates that drugs will be used off-label.[222] Moreover, drawing on *IMS Health*, the court found that prohibiting off-label promotion "paternalistically" interferes with both doctors' and patients' access to information about off-label use.[223] The court concluded that if "the government's objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal."[224] The court also concluded that restrictions on off-label promotion are not narrowly tailored to meet the government's interests and suggested several other ways to regulate off-label promotion that would intrude less on the First Amendment.[225]

The court noted that the FDCA makes it a crime to misbrand or conspire to misbrand a drug, but that the statute and its regulations do not expressly prohibit or criminalize off-label promotion.[226] To avoid conflict with the First Amendment, the court concluded that the FDCA should not be construed as criminalizing the simple promotion of a drug's off-label use.[227]

C. Judge Livingston's Dissent Provided Compelling Arguments That Restrictions on Off-Label Promotion Are Constitutional

The majority in *Caronia* suggested that a case in which off-label promotion is presented merely as evidence of the intent to misbrand

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222. *See id.*
223. *Id.*
224. *Id.* at 167.
225. *See id*. at 167–68. To seek a more limited and targeted approach to off-label promotion, the court suggested the following:

1. More directly address off-label use.
2. Guide physicians and patients to differentiate between misleading and false promotion and truthful or non-misleading promotion.
3. Develop warning or disclaimer systems or safety tiers within the off-label market to distinguish between drugs.
4. Require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval, enabling physicians, the government, and patients to track a drug's development.
5. Create other limits, including ceilings or caps on off-label prescriptions.
6. Further regulate the legal liability surrounding off-label promotion and treatment decisions, perhaps using medical malpractice and negligence theories of liability.
7. Prohibit off-label prescription altogether where such use is exceptionally concerning, as was done with human growth hormone.

See id. at 168.
226. *Id.* at 160.
227. *Id.*

could be successful.[228] At the same time, the court's analysis of the First Amendment challenge threatens to eviscerate the prohibition against misbranding—a prohibition that strikes at the very heart of the FDA's fundamental purpose. In a dissenting opinion, Judge Livingston made convincing arguments that *IMS Health* and *Western States* do not compel the result reached by the majority and that restrictions on off-label promotion are constitutional.[229]

1. Off-Label Promotion Is Evidence of Intent To Misbrand

Judge Livingston stated that Caronia's conviction should have been confirmed because his speech was evidence of his intent to misbrand.[230] Livingston cited the U.S. Supreme Court's decision in *Wisconsin v. Mitchell*, in which the Court recognized that the First Amendment "does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent."[231] She also cited a case decided by the U.S. Court of Appeals for the D.C. Circuit that concluded using speech "in the form of labeling" to infer intent is constitutionally permissible.[232] In *Whitaker v. Thompson*, the U.S. Court of Appeals for the D.C. Circuit addressed First Amendment issues similar to those in *Caronia*. A seller marketed saw palmetto extract as a treatment for enlarged prostate symptoms, claiming that the marketing statements he made were truthful and not misleading.[233] The court found that the statements about the product's intended use were drug claims, subject to the FDA approval process and consequently that the proposed label constituted speech about unlawful activity.[234] The court found that "a product's label may often be the only readily available evidence of the product's intended use."[235] In *Whitaker*, the court concluded that it is constitutionally

228. *See id.* at 172 (Livingston, J., dissenting).
229. *See id.* at 169–82.
230. *See id.* at 169.
231. *Id.* at 171 (quoting Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)).
232. *Id.* at 177 (quoting Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004)). The case involved the sale of saw palmetto, an extract from a dwarf American palm, and a dispute about the types of claims the seller could place on its label. The seller proposed a label that read: "Consumption of 320 mg daily of Saw Palmetto extract may improve urine flow, reduce nocturia and reduce voiding urgency associated with mild benign prostatic hyperplasia (BPH)." *Whitaker*, 353 F.3d at 948.
233. *See Whitaker*, 353 F.3d at 952.
234. *See id.* at 953.
235. *Id.* at 950.

permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining whether the seller's proposed sale of the product is illegal.[236] Judge Livingston maintained that the prosecution's reliance on Caronia's statements that Xyrem could be used to treat several off-label indications such as insomnia, periodic leg movement, Parkinson's and multiple sclerosis, were merely evidence of the intended uses and did not interfere with Caronia's First Amendment rights.[237]

Judge Livingston expressed concern as to whether the majority's reasoning would ever allow a conviction for misbranding.[238] The better reasoned analysis, she stated, would be to conclude that Caronia was prosecuted for misbranding and that his speech, the promotion of an off-label use, demonstrated his objective intent to introduce a misbranded drug into commerce.[239] In other words, "promotion of a use may demonstrate an objective intent that the drug be used for that purpose."[240] Even though doctors may legally prescribe for an off-label use, Livingston noted that "otherwise permissible conduct may become *impermissible* if undertaken with a prohibited motive, and speech may be used as evidence of such a motive."[241] Livingston provided the following example to illustrate:

> There might be no law forbidding the consumption of arsenic. But this would not endow Abby and Martha with a First Amendment right to offer arsenic-laced wine to lonely old bachelors with the intent that they drink it. And any statements Abby or Martha made suggesting their intent—even if all of the statements were truthful and not misleading—would not be barred from evidence by the First Amendment simply because arsenic might legally be consumed.[242]

2. Western States *and* IMS Health *Do Not Compel the Result Reached in* Caronia

Judge Livingston was not persuaded that the U.S. Supreme Court's decisions in *Western States* and *IMS Health* dictated the outcome reached by the majority in *Caronia*. She found that the cases are distinguishable because, in *Western States* and *IMS Health*, "[s]peech alone was sufficient

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236. *Id.* at 953.
237. *See Caronia*, 703 F.3d at 171–72 (Livingston, J., dissenting).
238. *Id.* at 172. The majority in *Caronia* stated that "[e]ven assuming the government can offer evidence of a defendant's off-label promotion to prove a drug's intended use and, thus, mislabeling for that intended use, that is not what happened in this case." *Id.* at 161 (majority opinion) (footnote omitted).
239. *See id.* at 173 (Livingston, J., dissenting).
240. *Id.* at 174.
241. *Id.* at 175.
242. *Id.* (referring to ARSENIC AND OLD LACE (Warner Brothers Pictures 1944)).

to trigger liability under the challenged statutes."[243] The FDA regulation challenged in *Western States* prohibited pharmacies from advertising or promoting the compounding of a particular drug.[244] In *IMS Health*, the statute targeted speech directly because it prohibited pharmaceutical manufacturers from using prescriber identifiable information for marketing or promotion.[245] In contrast, for a misbranding conviction, something more than just speech is required. Without evidence of intent to introduce the drug into commerce for an unapproved use, Caronia could not have been convicted of misbranding "no matter what he said."[246]

Judge Livingston also demonstrated that the FDCA's misbranding provisions can be distinguished from the content- and speaker-based scrutiny required by the U.S. Supreme Court in *IMS Health*. The dissent noted that *IMS Health* reaffirms the principle that restrictions on commercial speech may be constitutionally permissible because of the government's interest in protecting consumers from harm.[247] Regarding the content-based restrictions, the statute challenged in *IMS Health* was not aimed at preventing false or misleading speech; the FDA approval process, by contrast, seeks to prevent dangerous products with false and misleading labels from entering the market.[248] The heightened scrutiny for speaker based restrictions used in *IMS Health* is inapplicable to off-label promotion, according to Judge Livingston, because drug manufacturers are not a targeted group of speakers, as the majority in *Caronia* suggested, but rather "form the entirety of those speakers that could possibly undermine the new drug approval process by not participating in it."[249]

3. Off-Label Promotion Survives Central Hudson *Analysis*

According to Judge Livingston, the misbranding provisions of the FDCA survive constitutional scrutiny under the *Central Hudson* analysis because the provisions directly advance a substantial government interest and are narrowly drawn to further that interest.[250] Judge Livingston noted that the government's substantial interest in "preserving the effectiveness

243. *Id.* at 176.
244. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 370–71 (2002).
245. *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011).
246. *Caronia*, 703 F.3d at 176 (Livingston, J., dissenting).
247. *Id.* at 180 (citing *IMS Health*, 131 S. Ct. at 2672).
248. *Id.*
249. *Id.* at 179.
250. *Id.* at 177.

and integrity" of the FDCA's new drug approval process is not disputed.[251] Moreover, she called attention to cases in which the Court has recognized that "one of the FDCA's core objectives is to ensure that any product regulated by the FDA is safe and effective for its intended use."[252] Given these substantial interests, Judge Livingston found that allowing pharmaceutical representatives to promote off-label would discourage manufacturers from seeking approval for new uses, thereby calling into "question the very foundations of our century-old system of drug regulation."[253] Judge Livingston agreed with language in *Washington Legal Foundation* and *Caputo* that prohibiting off-label promotion is "'one of the few mechanisms available' to encourage participation in the approval process."[254] Furthermore, she maintained that "if drug manufacturers have a First Amendment right to distribute drugs for any use to physicians or even directly to patients, then the entire FDCA may well be unconstitutional."[255]

Judge Livingston concluded that the restrictions on off-label promotion are not more extensive than necessary.[256] In her dissent, she refuted each of the alternative regulations proposed by the majority as either ineffective or impractical.[257] Notably, she stated that a disclaimer system will still encourage manufacturers to bypass the approval process, and a ceiling or prohibition on off-label prescription would require extensive data tracking and could deny some patients the off-label use they need.[258]

Judge Livingston's dissent more accurately reflects Congress's concerns about the importance of the FDA approval process than does the majority

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251. *Id.* at 178 (citing Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002)). In *Western State*s, the Court stated, "Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process." *Western States*, 535 U.S. at 369.

252. *Caronia*, 703 F.3d at 177 (Livingston, J., dissenting) (quoting FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000)).

253. *Id.* at 169.

254. *Id.* at 178 (quoting Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *vacated in part sub nom.* Washington Legal Found. v. Henney, 202 F.3d 331, 337 (D.C. Cir. 2000)); *see also* United States v. Caputo, 517 F.3d 935, 940 (7th Cir. 2008) (pointing out that consumers and firms who do not desire to promote drugs or devices off-label would be worse off if the FDA could not prohibit off-label promotion).

255. *Caronia*, 703 F.3d at 179 (Livingston, J., dissenting).

256. *See id.* at 179–80.

257. *Id.*; *see supra* note 225 (listing some of the majority's suggestions for less restrictive means of meeting the government's interest in reducing the public's exposure to unsafe and ineffective drugs).

258. *See Caronia*, 703 F.3d at 179–80 (Livingston, J., dissenting).

opinion.[259] Moreover, the dissent echoes the warnings that some lower court decisions that have issued against sweeping too broadly where off-label promotion is concerned because prohibiting such behavior is one of the only mechanisms to incentivize drug manufacturers to seek FDA approval for new uses. In addition to Judge Livingston's strong arguments against the majority's decision, there are other critical factors about off-label promotion and the relationship between physicians and pharmaceutical salespeople that the court has not adequately addressed. In fact, several assumptions about the relationship between physicians and pharmaceutical companies that the U.S. Supreme Court relied on in *Western States* and *IMS Health* must be revisited to adequately address the dangers of off-label promotion.

IV. OFF-LABEL PROMOTION IS FALSE AND MISLEADING SPEECH

To avoid First Amendment concerns in prosecuting companies for off-label promotion, the government may be more successful in demonstrating that the specific speech at issue is not truthful and therefore not deserving of First Amendment protection. A more general approach is to show that restrictions on off-label promotion were put in place precisely because off-label promotion is inherently misleading.

In *Caronia*, the defendant maintained that he was prosecuted for *truthful*, off-label promotion. But the truthfulness of Caronia's statements was never at issue in the trial because the government believed it needed to show only that he promoted the drug for an off-label use.[260] Undoubtedly, the government could have presented evidence that Caronia's statements were false or misleading. For example, Caronia described Xyrem as a very safe drug with no contraindications, stating that "for the problems with insomnia there's no better drug, no safer drug, it's as safe as Ambien and Sonata."[261] As the government continues to pursue companies and individuals for off-label promotion, it may choose to avoid the First Amendment analysis by emphasizing the fraudulent nature of the speech rather than the more technical aspects of misbranding. The Ninth Circuit's decision in *United States v. Harkonen* provides an example of why this course may be more successful.[262]

259. *Id.* at 177.
260. *Id.* at 160 (majority opinion).
261. *Id.* at 172 n.3 (Livingston, J., dissenting).
262. *See* United States v. Harkonen, 510 F. App'x 633 (9th Cir. 2013) (per curiam).

A. United States v. Harkonen*: The First Amendment Does Not Protect Speech That Is Fraudulent or Inherently Misleading*

Although the *Caronia* decision purports to protect truthful, off-label speech, the U.S. Court of Appeals for the Ninth Circuit, in an unpublished per curiam decision, held that fraudulent off-label promotion is not deserving of First Amendment protection.[263] The decisions by the Ninth and Second Circuits do not create a clear circuit split because they addressed different issues related to off-label promotion. The *Harkonen* case dealt primarily with a charge of wire fraud and whether the jury could reasonably conclude that the defendant's speech was fraudulent.[264] The fraudulent nature of the speech, according to the Ninth Circuit, removed the case from First Amendment analysis.[265] Because the jury did not convict Harkonen on the misbranding charge, the Ninth Circuit did not address the interpretation of the misbranding provision that was central to the *Caronia* decision.[266] Because it is unpublished, the *Harkonen* decision is limited to the facts of the case.

In 2004, the U.S. Department of Justice began an investigation into the off-label marketing of the drug Actimmune.[267] The FDA approved the drug to treat two rare diseases that afflict approximately 800 Americans.[268] The company, InterMune, began marketing the drug off-label for idiopathic pulmonary fibrosis (IPF), a serious lung disease that affects some 200,000 Americans, with 50,000 new cases diagnosed each year.[269] There is no cure for IPF.[270] Unless patients receive a lung transplant, they usually die within two to five years.[271] Between 2000

263. *See id.* at 633.
264. *See id.* at 636.
265. *See id.*
266. United States v. Harkonen, No. C 08-00164 MHP, 2010 WL 2985257, at *2 (N.D. Cal. July 27, 2010).
267. United States v. Harkonen, No. C 08-00164 MHP, 2009 WL 1578712, at *1 (N.D. Cal. June 4, 2009).
268. *See id.*; Andrew Pollack, *Talking Up a Drug for This (and That)*, N.Y. TIMES, Apr. 27, 2003, at BU 3, *available at* http://www.nytimes.com/2003/04/27/business/talking-up-a-drug-for-this-and-that.html. In or around 1990, the FDA approved Actimmune to treat chronic granulomatous disease. In or around 2000, the FDA approved it to treat severe, malignant osteopetrosis. Both indications are rare disorders that primarily affect children. *Harkonen*, 2009 WL 1578712, at *1.
269. *Harkonen*, 2009 WL 1578712, at *1.
270. *Pulmonary Fibrosis*, AM. LUNG ASS'N, http://www.lung.org/lung-disease/pulmonary-fibrosis (last visited Aug. 25, 2014).
271. *See* Pollack, *supra* note 268.

and 2003, most sales of Actimmune were for the off-label treatment of IPF and sales increased from $11 million to $141 million.[272]

The off-label promotion of Actimmune for IPF was sparked by a paper published in 1999 in the *New England Journal of Medicine*.[273] The article indicated that, based on a small trial, Actimmune might be effective in treating IPF, but that a larger, more scientifically controlled study was needed to test the results.[274] Based on these results, InterMune began marketing the drug off-label. It also organized a larger in-house trial that included 330 patients. This trial showed that the drug was not effective in general.[275] In a subset of patients with milder disease, however, the trial showed that there might be encouraging results.[276]

The studies conducted by InterMune raised significant questions about how the data from such trials are interpreted. At trial, the jury heard testimony about the protocol for scientific studies and how the objectives of a study are defined.[277] Although the protocol for a study can be changed after the study begins, a final protocol must be in place before the data is made available to the researchers to prevent manipulation of the data.[278] The protocol for the IPF trial involved one primary endpoint: "progression-free survival time."[279] The study missed its primary endpoint. In other words, Actimmune was not effective in halting the progression or increasing the survival time for IPF patients.[280] The trial also had ten secondary endpoints, all of which it missed.[281] If a primary endpoint fails, secondary endpoints are considered to be "hypothesis generating," providing

272. *Harkonen*, 2009 WL 1578712, at *3. Anecdotal information from patients who used Actimmune for IPF is mixed. One patient accused Harkonen of publishing "an outright lie." The patient injected himself with Actimmune every other day for eighteen months, at a cost of $6000 a month for the drug. He believes that subsequent clinical trials indicated the drug was not only ineffective, but that it exposed hundreds of patients to serious risks. He also stated that "[c]reating false hope is a serious crime, let alone exposing someone to these risks." *See* Mike Henderson, *Patient's View on Actimmune CEO Sentence*, GOOD PROMOTIONAL PRACTICES (May 5, 2011), http://goodpromotional practices.com/2011/05/05/what-about-the-patients.

273. *See Harkonen*, 2009 WL 1578712, at *2.

274. *Id.*

275. *Harkonen*, 2010 WL 2985257, at *4; *Harkonen*, 2009 WL 158712, at *2.

276. *See Harkonen*, 2010 WL 2985257, at *4.

277. *Id.*

278. *Id.*

279. *Id.* at *5.

280. *See id.* at *9.

281. *Id.* at *7.

information to be tested in future trials.[282] Nevertheless, InterMune focused on the data generated by secondary endpoints and subgroup analyses.[283]

The government alleged that beginning in the fall of 2000, Dr. Harkonen, the CEO of InterMune, and others at the company, misrepresented the import of the data from the trial to promote the drug for IPF.[284] Focusing on results from a subset of patients, Dr. Harkonen issued a press release with the headline, "InterMune announces Phase III data demonstrating survival benefit of Actimmune in IPF," followed by "Reduces Mortality by 70% in Patients with Mild to Moderate Disease."[285] The court explained that "the jury could have found that Harkonen's choice of words in the press release implied causation between Actimmune and the survival of IPF patients, when the data from the study objectively did not establish any such certain and/or verifiable relationship."[286] Before the press release was issued, many sources had told Harkonen that the trial missed its primary endpoint as well as all ten secondary endpoints.[287] Harkonen was told that the subgroup analysis results focusing on mild to moderate IPF patients were "unreliable and inconclusive."[288] InterMune's Senior Director of Biostatistics testified that "post-hoc analyses are 'good science' in the sense that they may generate hypotheses for future study, but that he 'winced' when he saw the Press Release because 'the conclusiveness of the results was overstated.'"[289]

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282. *See id.* In *Bad Pharma*, Ben Goldacre explains the danger of changing outcomes from trials by people who "switch their primary outcomes," as well as the problems involved in subgroup analyses. *See* BEN GOLDACRE, BAD PHARMA: HOW DRUG COMPANIES MISLEAD DOCTORS AND HARM PATIENTS 200–12 (2012).

283. *See Harkonen*, 2010 WL 2985257, at *9–10.

284. United States v. Harkonen, No. C 08-00164 MHP, 2009 WL 1578712, at *2 (N.D. Cal. June 4, 2009).

285. *Id.*

286. *Harkonen*, 2010 WL 2985257, at *9. The court elaborated:

> The jury heard credible testimony that in clinical trials with multiple endpoints, where the primary endpoint is missed, and where researchers conduct post-hoc, subgroup analyses, p-values are unreliable. Thus, depending on the context, sub-0.05 p-values do not "demonstrate", prove, establish or indicate anything. Under such circumstances, secondary endpoint and post-hoc, subgroup analyses can only be used in an exploratory manner, providing researchers with some indication about additional relationships between a drug and a condition that might warrant further investigation. The press release, however, equates a p-value of less than 0.05 with statistical significance, causation and efficacy without any adjustment for context, including for secondary endpoints and post-hoc analyses.

Id.

287. *Id.* at 12.

288. *Id.*

289. United States v. Harkonen, 510 F. App'x 633, 638 (9th Cir. 2013) (per curiam).

The company distributed the press release to sales representatives with instructions on how to discuss it with doctors.[290] The company also hired a marketing firm to explore how pulmonologists would react to the information.[291] Sales representatives, complete with incentive and bonus plans related to sales of Actimmune for IPF, were sent to detail pulmonologists.[292]

Harkonen was indicted for disseminating information regarding Actimmune for the treatment of IPF with the intent to defraud and mislead, and causing Actimmune to be misbranded.[293] He was convicted on a charge of wire fraud but found not guilty on the misbranding count.[294] Harkonen appealed his conviction, arguing that the press release was speech protected by the First Amendment.[295]

The Ninth Circuit began with the proposition that the First Amendment does not protect fraudulent speech.[296] In a recent case, the U.S. Supreme Court cited fraud as one of the long recognized categories of content-based speech that may be restricted.[297] Thus, the Ninth Circuit focused on whether facts found by the jury established that the press release was fraudulent. The court found that the evidence supported the conclusion that the press release was misleading, that Harkonen knew it was misleading, and that he had the specific intent to defraud.[298] At trial, witnesses testified that the press release misrepresented the results of the company's in-house trial and that Harkonen had prevented InterMune's

290. United States v. Harkonen, No. C 08-00164 MHP, 2009 WL 1578712, at *2 (N.D. Cal. June 4, 2009).
291. *Id.*
292. *Id.*
293. *Id.* at *1.
294. United States v. Harkonen, No. C 08-00164 MHP, 2010 WL 2985257, at *1 (N.D. Cal. July 27, 2010).
295. United States v. Harkonen, 510 F. App'x 633, 635–36 (9th Cir. 2013) (per curiam).
296. *Id.* at 636 (citing United States v. Alvarez, 132 S. Ct. 2537, 2544 (2012)).
297. *Alvarez*, 132 S. Ct. at 2544 (citing Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 771 (1976)). In *Alvarez*, however, the Court held that the defendant's false statements about receiving the Congressional Medal of Honor were protected by the First Amendment and that the Stolen Valor Act, which criminalized such false statements, was unconstitutional. *See id.* at 2551. According to the Court, "the law allows content-based regulation of speech" in only a "few categories"; it does not allow "any general exception to the First Amendment for false statements." *Id.* at 2544.
298. *See Harkonen*, 510 F. App'x at 636–37.

clinical personnel from seeing the press release prior to publication.[299] He also sought to hide the analysis of the trial data from the FDA, stating that he "didn't want to make it look like we were doing repeated analyses looking for a better result."[300] The court found that Harkonen's statement that he would "cut that data and slice it until he got the kind of results he was looking for" showed specific intent to defraud.[301]

Harkonen maintained that the First Amendement protected his statements because they involved scientific debate and were beyond the reach of the wire fraud statute.[302] This argument rested on a 1902 U.S. Supreme Court decision, *American School of Magnetic Healing v. McAnnulty*, which held that genuine debates over whether a given treatment caused a particular effect are outside the scope of the mail and wire fraud statutes.[303] The Ninth Circuit found that *McAnnulty* does not prohibit all prosecutions based on fraudulent statements about the efficacy of a drug.[304] The court cited the Supreme Court's decision in *Seven Cases v. United States*, in which the Court found that "false and fraudulent representations may be made with respect to the curative effect of substances."[305] Harkonen also argued that "his statements were fraudulent only if they were universally considered objectively false."[306] The court rejected the argument, stating that "the term 'to defraud' has its commonplace definition and includes any sort of 'dishonest method or scheme,' and any 'trick, deceit, chicane or overreaching.'"[307] Finally, the court rejected Harkonen's argument that "he was engaging in a genuine scientific debate," concluding that "genuine debates of any sort are, by

299. *See id.* at 636.
300. *Id.*
301. *Id.*
302. *Id.* at 637.
303. *See id.* (referencing Am. School of Magnetic Healing v. McAnnulty, 187 U.S. 94 (1902)).
304. *See id.*
305. *Id.* (quoting Seven Cases of Eckman's Alterative v. United States, 239 U.S. 510, 517 (1916)). In *Seven Cases*, the Court considered misbranding charges against a company that purportedly made false and fraudulent statements about a product. A circular mailed with the product stated, "We know it has cured and that it has and will cure Tuberculosis," and "Effective as a preventative for Pneumonia." *Seven Cases*, 239 U.S. at 514. The Court emphasized that the statements accompanying the product were "false and fraudulent." *Id.* at 517. The Court distinguished between the owner's right to "give his views regarding the effect of his drugs" and "false and fraudulent representations." *Id.* at 517–18. The Court stated, "Congress recognized that there was a wide field in which assertions as to curative effect are in no sense honest expressions of opinion but constitute absolute falsehoods and in the nature of the case can be deemed to have been made only with fraudulent purpose." *Id.* at 518. As in *Harkonen*, *supra*, the Court emphasized the "actual intent to deceive." *Id.* at 519.
306. *Harkonen*, 510 F. App'x at 637.
307. *Id.* (quoting Carpenter v. United States, 484 U.S. 19, 27 (1987)).

definition, not fraudulent."[308] In short, the court found that the jury had considered conflicting scientific information and found that Harkonen's statements about Actimmune's efficacy for treating IPF were misleading.[309]

As an unpublished opinion, the Ninth Circuit's decision is limited to its facts. But the decision provides useful information for future prosecutions involving off-label promotion.[310] *Harkonen* suggests that cases involving off-label promotion are likely to be most successful when the fraudulent nature of a marketing scheme is clear and compelling.

B. Prohibiting Misbranding as False and Misleading

The Court has stated clearly that information that is "false or misleading in any way" whether "commercial or otherwise" is not protected under the First Amendment,[311] and that the government is "free to prevent the dissemination of commercial speech that is false, deceptive, or misleading . . . or that proposes an illegal transaction."[312] The Court has gone farther, stating that governments may "ban commercial expression that is fraudulent or deceptive without further justification."[313] Thus, in seeking to prohibit off-label promotion, the government would be wise to emphasize the illegality of misbranding as well as the false, deceptive, or misleading nature of the information provided by detailers.

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308. *Id.*

309. *See id.*

310. While other cases alleging false statements in off-label promotion have not reached the courts, companies have admitted to making false statements to doctors pursuant to off-label marketing strategies. For example, Purdue Pharma, the manufacturer of OxyContin, acknowledged that its sales representatives had made false statements to doctors, claiming that OxyContin was more resistant to abuse and less likely to cause addiction than competing products. *See* 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, 1262–64 (2008). The company promoted OxyContin for use every eight hours instead of the twelve hours approved by the FDA. *Id.* at 1262. The company paid $19.5 million to states to settle a civil suit based on its alleged promotion of off-label use. *Id.* Purdue Pharma also paid $470 million in fines and payments to state and federal agencies and $130 million to settle civil lawsuits brought against the company by former patients who claimed to have become addicted to OxyContin. *Id.* at 1263. The $600 million the company paid in fines and civil penalties was about ninety percent of the profits it made from its initial OxyContin sales. *Id.*

311. Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 771 (1976).

312. *See, e.g.*, Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 638 (1985).

313. *See, e.g.*, Edenfield v. Fane, 507 U.S. 761, 768 (1993).

In *Western States*, the Court stated, "we ask as a threshold matter whether [a pharmacy's] commercial speech . . . is misleading. If so, then the speech is not protected by the First Amendment."[314] But in *Western States*, *IMS Health*, and *Caronia*, the government did not assert that the defendant's speech was false or misleading. In *IMS Health*, the Court stated, "the State nowhere contends that detailing is false or misleading within the meaning of this Court's First Amendment precedents. . . . Nor does the State argue that the provision challenged here will prevent false or misleading speech."[315] The information at issue in both *Western States* and *IMS Health* involved verifiable factual information. In *Western States*, the information at issue involved advertising that a particular compounder made a particular product;[316] in *IMS Health*, the information involved which drugs particular doctors prescribed.[317] In *Caronia*, the government likely could have asserted that the information the defendant provided about Xyrem was false and misleading. Based on its construction of the misbranding statute, however, the government presumed that it needed to show only that the defendant had conspired to misbrand the drug.[318] Given the uncertainty of the Court's analysis of commercial speech—the "heightened scrutiny" introduced in *IMS Health*, as well as what one justice termed the "unforgiving" version of *Central Hudson* introduced in *Western States*,[319] the government should present cases involving off-label promotion through detailing as false and inherently misleading.

A common sense approach to the issue of off-label detailing is arguing the practice is inherently misleading. One author maintains that marketing strategies such as detailing have no purpose other than to "pervert evidence-based decision-making in medicine."[320] U.S. Supreme Court precedent provides some hope for this argument, but poses challenges as well. The nature of in-person solicitation by detailers makes the practice particularly susceptible to fraudulent and misleading information. In *Ohralik v. Ohio State Bar Association*, the Court recognized that "face-to-face" solicitation by a lawyer might lead to problems such as "undue influence" and "fraud."[321] In *Ohralik*, the Court also noted that in-person

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314. Thompson v. W. States Med. Ctr., 535 U.S. 357, 367 (2002).
315. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2672 (2011).
316. *See Western States*, 535 U.S. at 357.
317. *See IMS Health*, 131 S. Ct. at 2659.
318. United States v. Caronia, 703 F.3d 149, 158 (2d Cir. 2012).
319. *See IMS Health*, 131 S. Ct. at 2679 (Breyer, J., dissenting).
320. *See* GOLDACRE, *supra* note 282, at 246.
321. 436 U.S. 447, 448, 464 (1978). The Court held that a state has the right to discipline attorneys "for soliciting clients in person, for pecuniary gain, under circumstances likely to pose dangers that the State has a right to prevent." *Id.* at 447.

solicitation presents unique regulatory difficulties because it is "not visible or otherwise open to public scrutiny."[322] Such solicitations, the Court stated, are "one-sided" and may encourage "uninformed decisionmaking."[323] The Court concluded that rules prohibiting in-person solicitation by lawyers are "prophylactic measures whose objective is the prevention of harm before it occurs."[324]

Ideally, courts should recognize that a prophylactic rule prohibiting off-label promotion is necessary. Some of the problems associated with in-person solicitation by lawyers resonate with off-label promotion through detailing. The face-to-face nature of the communication by detailers is a one-sided presentation, not visible to public scrutiny that may lead to uninformed, or at least misinformed, decisionmaking. In *Caronia*, the court assumed that information about off-label use, provided to prescribing physicians "can save lives" because it provides a basis for "intelligent and well-informed" decisions.[325] This assumption, however, fails to account for the very nature and purpose of detailing. Because conversations between sales representatives and doctors take place largely in private, they are difficult to monitor and thus it is impossible to know the extent to which information is truthful or misleading.[326] Although economic incentives certainly do not remove off-label promotion from First Amendment protection, the reliability of the information must be considered in the context of a sales force incentivized to sell for off-label use and a company intent on avoiding the costly FDA approval process.[327]

The Court had previously held that states could not prohibit truthful advertising about legal services because it impermissibly inhibited the free flow of commercial information under the First Amendment. *See* Bates v. State Bar of Arizona, 433 U.S. 350 (1977). The Court found that advertising by lawyers is not inherently misleading, but recognized that there that might be some advertisements that would be misleading "because the public lacks sophistication concerning legal services." *Id.* at 383. In particular, the Court noted that advertisements that "are not susceptible of measurement or verification," such as claims about the quality of services provided or in-person solicitations, "may be so likely to be misleading as to warrant restriction." *Id.* at 383–84.

322. *Ohralik*, 436 U.S. at 466.

323. *Id.* at 457.

324. *Id.* at 464.

325. United States v. Caronia, 703 F.3d 149, 167 (2d Cir. 2012).

326. *See* Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 N. ENG. J. MED. 1557, 1558 (2009), *available at* http://www.hsph.harvard.edu/michelle-mello/files/2012/09/Off-label_PDF.pdf.

327. *See* Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 762 (1976).

Furthermore, prohibitions on off-label promotion seek to prevent harm before it occurs, by insuring that drugs are properly tested for safety and efficacy.

Although these factors should persuade courts of the dangers of off-label promotion and the necessity of restrictions, the U.S. Supreme Court, with the exception of the *Ohralik* decision, has been hostile to "prophylactic" rules.[328] Moreover, in *Ohralik*, the Court emphasized the vulnerability of distressed potential clients.[329] By contrast, courts have viewed doctors, the targets of detailing, as sophisticated customers.[330] Though there are meritorious arguments about the lack of sophistication of doctors in response to detailing, as well as the training of detailers in the art of persuasion, such arguments require educating the courts about how detailing impacts the prescribing habits of doctors to the detriment of the public health.[331]

A stronger argument for restricting off-label promotion through detailing is that statements made by detailers about off-label use are not by their very nature subject to verification. Several statements by the Supreme Court indicate that information that cannot be verified is inherently misleading. In the context of legal advertising, the Court recognized the danger of statements that are not verifiable, stating that "the indeterminacy of statements about law makes it impractical if not impossible to weed out accurate statements from those that are false or misleading."[332] The Court has also stated that "[r]egulations that suppress the truth are no less troubling because they target objectively verifiable information."[333] Information about the safety and efficacy of off-label uses is not verifiable in any scientific way.

Judge Kozinski, a proponent of eliminating the distinction between commercial and noncommercial speech, has recognized that "listeners are far less likely to be misled about matters they can check out by reference to objective facts than about such intangibles as the leadership qualities

328. *See, e.g.*, Edenfield v. Fane, 507 U.S. 761, 777 (1993). In *Edenfield*, the Court held that a state ban on personal solicitation by Certified Public Accountants was unconstitutional. *Id.* The Court did not find the risks associated with in-person solicitation by attorneys were present in cases involving CPAs. The Court stated, "Broad prophylactic rules in the area of free expression are suspect. Precision of regulation must be the touchstone in an area so closely touching our most precious freedoms." *Id.* (quoting NAACP v. Button, 371 U.S. 415, 438 (1963)).

329. See *Ohralik*, 436 U.S. at 465–66.

330. *See, e.g.*, Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011).

331. *See* discussion *infra* Part IV.B.

332. Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 644 (1985).

333. 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 502 (1996).

of a political candidate or the divine inspiration of a television evangelist."[334] Judge Kozinski stated:

> [M]uch scientific expression can easily be labeled true or false, but we would be shocked at the suggestion that it is therefore entitled to a lesser degree of protection. If you want, you can proclaim that the sun revolves around the earth, that the earth is flat, that there is no such thing as nitrogen, that flounder smoke cigars, that you have fused atomic nuclei in your bathtub—you can spout any nonsense you want, and the government can't stop you.[335]

The argument that detailers' speech about off-label use is protected under the First Amendment as scientific opinion is easily defeated, as the *Harkonen* case demonstrated.[336] Furthermore, Judge Kozinski's presumption that "much scientific expression can easily be labeled true or false"[337] is a matter of degree. The safety and efficacy of a drug for off-label use cannot be "checked out" by consumers. Even doctors find it difficult to verify such information as data is uniquely within the control of the pharmaceutical company.

What is clear from both *Western States* and *IMS Health* is the Court's concern for the free flow of information and an informed public.[338] In asserting that off-label promotion is false and misleading, the government must emphasize that the goal of such restrictions is consistent with First Amendment jurisprudence—to provide accurate information to both doctors and patients. Although the Court's decision in *IMS Health* indicates that it does not see the practice of detailing in general as problematic, even when it influences doctors' prescribing habits, the Court should recognize that detailing involving off-label promotion carries unique and substantial risks.[339]

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334. Alex Kozinski & Stuart Banner, *Who's Afraid of Commercial Speech?*, 76 VA. L. REV. 627, 636–37 (1990) (arguing that there is no basis for the distinction between commercial and noncommercial speech in the text or history of the Constitution and that there is no valid reason for the distinction). *But see* Christopher P. Guzelian, *Scientific Speech*, 93 IOWA L. REV. 881, 910 (2008) ("[C]ommunicators who offer misleading scientific opinions cannot invariably enjoy First Amendment protection if those opinions cause recognized legal injuries.").

335. Kozinski & Banner, *supra* note 334, at 635.

336. *See supra* text accompanying notes 303–09.

337. Kozinski & Banner, *supra* note 334, at 635.

338. *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2664 (2011); Thompson v. W. States Med. Ctr., 535 U.S. 357, 366–67 (2002).

339. *See IMS Health*, 131 S. Ct. at 2671.

The argument that promotional information about off-label uses is inherently misleading is part and parcel of the FDA's regulatory scheme. Congressman Henry A. Waxman identified three features of the pre-1962 regulatory scheme that caused promotional claims about unproven uses to be considered inherently misleading:

> 1) physicians heavily relied on promotional information from manufacturers, much of which was misleading; 2) existing reliable, objective evidence was difficult or impossible for average physicians to find because they were too busy to track down scattered, often unpublished data on hundreds of new drugs; and 3) in the absence of required testing, few, if any, companies conducted the kind of studies that would provide reliable evidence of their products' effectiveness.[340]

Off-label promotion is precisely the type of "unsubstantiated" promotion that concerned Waxman. Because doctors may lawfully prescribe off-label, it is essential for detailers to reach them and evidence shows that doctors rely on information provided by detailers. It is difficult or impossible to obtain objective information about off-label use and effectiveness because the very reason for off-label promotion is often to avoid the rigorous testing that the FDA requires. One author has wisely suggested that when manufacturers raise truthfulness as a defense, the manufacturer should bear the burden of proving the truthfulness of its off-label claim.[341]

In *Caronia*, the court stated that prohibiting off-label promotion "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information."[342] The court also stated that the public interest is furthered when information that can "save lives" is provided, including information about off-label use.[343] The court's view of detailing suggests that pharmaceutical representatives are educators who provide truthful, nonmisleading information to doctors and that the risks of influencing prescribing habits are few because physicians are "sophisticated and experienced customers."[344] Yet the medical literature reveals that detailing is not designed to educate physicians but rather is calculated to sell products by influencing doctors' prescribing habits.[345] In

340. Waxman, *supra* note 1, at 306 (citations omitted).

341. *See* Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 572 (2014).

342. United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012).

343. *Id.* at 167.

344. *Id.* at 166 (quoting Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670–71 (2011) ("The fear that physicians, sophisticated and experienced customers, would make bad decisions if given truthful information' cannot justify content-based burdens on speech.")).

345. *See* Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, PLOS MED. 2

describing how detailing works, through the lens of sales representatives and physicians, the following subparts demonstrate that off-label promotion is inherently misleading. Allowing off-label promotion guts the FDA's premarketing approval system. It introduces unreliable information into the marketplace of ideas, information that neither doctors nor the public can access or assess. Because only the detailers themselves and the doctors they target participate in the conversation, off-label marketing strategies come to light almost exclusively through information provided by company insiders or physicians.[346]

1. How Detailers Mislead Doctors

In *IMS Health*, the Court stated: "There are divergent views regarding detailing and the prescription of brand-name drugs. Under the Constitution, resolution of that debate must result from free and uninhibited speech."[347] The Court refers to "brand-name drugs" and, presumably, to detailing for FDA-approved uses, that have been tested for safety and efficacy. This subpart examines information from doctors and sales representatives about the impact of detailing and off-label promotion on medical decisions, demonstrating that "free and uninhibited speech" in the context of promoting drugs for off-label use leads to decisions based on marketing rather than scientific evidence, a practice that should concern courts.

Dr. Jerome P. Kassirer, a Professor at the Tufts University School of Medicine, finds the idea that sales representatives present truthful, nonmisleading information to physicians to be highly problematic.[348] Dr. Kassirer asserts that "[t]he notion that this is all for physician education is nonsense" and the fact that companies spend so much money on advertising is evidence of their intent to influence physicians.[349] Several researchers have concluded that the pharmaceutical industry spends

(Apr. 5, 2011), http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000431.

346. *See id.*

347. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011).

348. *See* Marcus Baram, *Ex-Drug Sales Rep Tells All*, ABC NEWS (Mar. 13, 2008), http://abcnews.go.com/Health/Story?id=4438095&page=1.

349. *See id.*

more money on marketing than on research and development.[350] In 2000, pharmaceutical firms reportedly spent a total of $8.5 billion on marketing, with most of the money financing physician-industry interactions.[351] A 2008 report estimated that companies spend as much as $57.5 billion on advertising, double what they spend on research.[352] The importance of a manufacturer's detailing sales force is reflected in the fact that it consumes the largest portion of the marketing budget, a budget that exceeds that of any other U.S. industry.[353] In 2008, pharmaceutical companies reportedly spent $12 billion on detailing to physicians and other health care professionals.[354] There is some evidence that marketing to physicians is more profitable than direct-to-consumer advertising because detailing increases sales for the particular brand of drug promoted, rather than raising awareness or creating demand across brands, as direct-to-consumer advertising tends to do.[355]

The industry's faith in detailing is evident in the growth of the number of drug representatives in the United States.[356] Between 1995 and 2005,

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350. *See, e.g.*, Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL'Y L. & ETHICS 785, 785 (2005).

351. *See* Alice LaPlante, *Marketing Directly to Physicians Reaps Higher Returns for Drug Companies*, STAN. GRADUATE SCH. BUS. (Aug. 1, 2006), http://www.gsb.stanford.edu/news/research/mktg_narayanan_pharmaceuticals.shtml.

352. *See* Marc-André Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, PLOS MED. 32 (Jan. 3, 2008), http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.0050001&representation=PDF. The pharmaceutical industry disputes such figures, maintaining that it spends more on research and development than on all combined promotional activities. *See* PHRMA, THE FACTS ABOUT PHARMACEUTICAL MARKETING & PROMOTION 17–18 (2008), *available at* http://www.phrma.org/sites/default/files/pdf/marketing_and_promotion_facts_071108_final.pdf.

353. Manchanda & Honka, *supra* note 350, at 785 (citing DICK R. WITTINK, ANALYSIS OF ROI FOR PHARMACEUTICAL PROMOTION (ARPP) (2002), *available at* http://www.rxpromoroi.org/ar'pp/media/arpphandout0927.pdf).

354. CONG. BUDGET OFFICE, PROMOTIONAL SPENDING FOR PRESCRIPTION DRUGS 2 (2009), *available at* http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/105xx/doc10522/12-02-drugpromo_brief.pdf.

355. *See* LaPlante, *supra* note 351; Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373, 373 (2000).

356. *See* Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 309–16 (1992). In *Bad Pharma*, Dr. Ben Goldacre states that:

> the overwhelming majority of the industry's promotional budget goes on influencing doctors, rather than patients, and about half of that gets spent on drug reps. They are not cheap, and though their numbers fluctuate, they have doubled in the past two decades, with one rep for every three to six doctors, depending on how you measure it.

GOLDACRE, *supra* note 282, at 274 (footnotes omitted).

the number of pharmaceutical sales representatives increased from 38,000 to 100,000.[357] Studies suggest that this number would furnish one sales representative for every six physicians, but that the actual ratio is closer to one sales representative per 2.5 doctors because not all physicians practice and physicians who are unlikely to change their prescribing habits are not detailed.[358] Researchers have summarized the value of detailers to doctors as follows:

> [T]he concept that reps provide necessary services to physicians and patients is a fiction. Pharmaceutical companies spend billions of dollars annually to ensure that physicians most susceptible to marketing prescribe the most expensive, most promoted drugs to the most people possible. The foundation of this influence is a sales force of 100,000 drug reps that provides rationed doses of samples, gifts, services, and flattery to a subset of physicians. If detailing were an educational service, it would be provided to all physicians, not just those who affect market share.[359]

Although the Court's decision in *IMS Health* suggests that it is not perturbed by the influence that detailing has on doctors' prescribing habits,[360] the Court should recognize the unique role that detailing plays in off-label promotion. Detailing is particularly important in off-label promotion because doctors are allowed to prescribe for off-label uses. Abbott Laboratories' off-label promotion of its drug Depakote provides an example of the important role that detailing plays.[361] The company admitted that for eight years it had a sales force dedicated to marketing Depakote for off-label uses.[362] The drug was FDA-approved for use with epileptic seizures, bipolar mania, and migraines, but was marketed to

357. Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, PLOS MED. 624 (Apr. 24, 2007), http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.0040150&representation=PDF.

358. *Id.*

359. *Id.* at 625.

360. In *IMS Health*, the Court noted that the Vermont legislature had concluded that the information the pharmaceutical marketers provide to doctors is incomplete and unbiased. Furthermore, the legislature concluded that doctors rely on this information because they do not have time to research the constant advances in drugs. Nevertheless, the Court spoke with seeming approval of the detailing as "an expensive undertaking" and recognized that detailers can be more effective when they know a physician's prescribing practices. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2660–61 (2011).

361. *See* Press Release, U.S. Dep't of Justice, Abbott Labs To Pay $1.5 Billion To Resolve Criminal and Civil Investigations of Off-Label Promotion of Depakote (May 7, 2012), *available at* www.justice.gov/opa/pr/2012/May/12-civ-585.html.

362. *See id.*

nursing homes to treat symptoms of dementia in elderly patients.[363] There was no scientific evidence that the drug was effective in controlling dementia.[364] Furthermore, even as Abbott began its off-label campaign, it had halted a trial for treating dementia because of side effects such as dehydration and anorexia.[365] The company pled guilty and agreed to pay $1.5 billion for misbranding the drug.[366] Even without evidence of the drug's safety or efficacy in treating particular conditions, the sales force, through detailing, was able to convince doctors to prescribe it for these uses.

In assessing speech related to pharmaceutical promotional activities, courts have emphasized that information is power and that manufacturers are in the best position to provide relevant information.[367] This argument, however, overstates the scientific expertise of sales representatives and gives insufficient weight to the pressures on sales representatives to sell. The information that sales representatives provide is more likely to be biased than truthful. They are trained to emphasize the benefits of their product, to suppress any negative information about their product, and to highlight negative aspects of a competitor's product.[368] Thus, although manufacturers are in a unique position to provide information to the medical community, they are more likely to control the information in a manner that best advances sales.[369]

Detailers are trained to target doctors most susceptible to marketing efforts and to develop a relationship with them.[370] To ensure detailers

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363. *See id.*
364. *See id.*
365. *See id.*
366. *See id.*
367. *See* United States v. Caronia, 703 F.3d 149, 166–67 (2d Cir. 2012).
368. *See* Michael A. Steinman & Dean Schillinger, *Drug Detailing in Academic Medical Centers: Regulating for the Right Reasons, with the Right Evidence, at the Right Time*, 10 AM. J. BIOETHICS 21, 23 (2010); *see also* Baram, *supra* note 348 ("To sell their drugs, pharmaceutical companies . . . exaggerate the drug's benefits and underplay their side-effects . . . ."); Letter from Shahram Ahari, Former Eli Lilly Pharm. Sales Representative, to Congress (March 2008), *available at* http://www.aging.senate.gov/imo/ media/doc/hr190 sa.pdf (explaining that drug representatives were trained to downplay side effects of a drug).
369. Peter Doshi and Tom Jefferson raise a related issue about manufacturers' control of information in *Drug Data Shouldn't Be Secret*, N.Y. TIMES (April 10, 2012), http://www.nytimes.com/2012/04/11/opinion/drug-data-shouldnt-be-secret.html?_r=0. The authors criticize the drug manufacturer, Roche, for failing to release to the research community most of the clinical trial data that would support claims about the anti-influenza drug Tamiflu. *Id.* They note that the FDA-approved Tamiflu to treat flu symptoms but did not reach conclusions about Tamiflu's ability to reduce hospitalization stays and serious complications. *Id.* The authors suggest that literature, including peer-reviewed articles, touting the "assumed properties" of the drug, rely solely on information published by Roche. *Id.* More than $1.5 billion of taxpayer money was devoted to stockpiling the drug without any evidence of the drug's effectiveness. *Id.*
370. *See* Ahari, *supra* note 368.

will connect socially with doctors, job qualifications are more likely to include an outgoing personality and keen observation skills than an education or training in science.[371] A former drug representative for Eli Lilly described drug representatives as "young and attractive" and "eloquent and convincing," but lacking in "any significant scientific understanding."[372] He also stated that representatives usually change jobs relatively quickly as enthusiasm about the product diminishes, and that they are "easily replaced by other, younger, less questioning recruits."[373]

Sales representatives are tasked with identifying doctors who are likely to change their prescribing habits and finding ways to make them do so. They develop profiles of doctor that will help them create a social relationship to increase influence.[374] Detailers may bestow free samples, invitations to speak at various events, dinners, and expense-paid trips to doctors who write large numbers of prescriptions.[375] Even small gifts such as pens bearing the company's logo are effective in developing "reciprocity," the term well-known in psychology and marketing for creating an obligation, whether conscious or subconscious, to return a favor.[376] Dr. Ben Goldacre summarizes how a drug company perceives a doctor's prescribing decisions:

> You want the doctor to prescribe your product, and you will do everything you can to make that happen. You might dress this up as "raising awareness of our product," or "helping doctors make decisions," but the reality is, you want sales. So you will advertise your new treatment in medical journals, stating the benefits but downplaying the risks, and leaning away from unflattering comparisons. You will send out "drug reps" to meet doctors individually, and

371. *See id.*

372. *See id.* Ahari testified that in the training class for the "elite neuroscience division" at Eli Lilly, none of his twenty-one classmates had college level scientific education. *Id.*

373. *Id.*

374. See GOLDACRE, *supra* note 282, at 277–79.

375. Shane M. Ward, WLF *and the Two Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet*, 56 FOOD & DRUG L.J. 41, 47–48 (2001).

376. *See* ASS'N OF AM. MED. COLLS., THE SCIENTIFIC BASIS OF INFLUENCE AND RECIPROCITY: A SYMPOSIUM 1 (2007), *available at* https://members.aamc.org/eweb/upload/The%20Scientific%20Basis%20of%20Influence.pdf; *see also* GOLDACRE, *supra* note 282, at 281 (footnote omitted) (stating that social science research shows that "doctors develop an unconscious sense of obligation, a debt to be repaid, especially when stronger relationships are built through social events").

> talk up the merits of your treatment. They will offer gifts, lunches, and forge personal relationships that may be mutually beneficial later.[377]

Most people would assume, as the court did in *Caronia*, that doctors can readily distinguish sales pitches from reliable scientific data. The next subpart explores how doctors, many of whom believe they are impervious to sales pitches and token gifts, are influenced by such tactics in a manner that jeopardizes the public health.

2. Doctors Are Not "Sophisticated and Experienced Customers" Able To Distinguish Between Valid and Misleading Information

Courts have largely assumed that doctors are capable of distinguishing valuable, scientific information from misleading claims about pharmaceutical products.[378] Thus, in *Washington Legal Foundation v. Henney*, the court rejected the argument that the government had an interest in ensuring that physicians receive a balanced flow of information.[379] The court stated that "[t]he government, however benign its motivations, simply cannot justify a restriction of truthful nonmisleading speech on the paternalistic assumption that such restriction is necessary to protect the listener from ignorantly or inadvertently misusing the information," especially when the "recipient of information is a sophisticated listener trained extensively in the use of such information—as are the doctors and other health care providers in this case."[380] Similarly, in *United States v. Caputo*, the district court stated that it could not find off-label promotion to be inherently misleading because physicians are a sophisticated audience, and are able to "independently evaluate the validity of [sales representatives'] claims."[381] In *IMS Health*, the Court referred to prescribing physicians as "'sophisticated and experienced' consumers."[382] In *Caronia*, the court echoed that language.[383]

The conclusions that courts have made about doctors' ability to discern valuable from misleading information is hard to understand because the reasons for current restrictions on promotion were extensively addressed

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377. GOLDACRE, *supra* note 282, at 244.

378. *See* United States v. Caputo, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003) ("Defendants' speech was directed at physicians who are familiar with the FDA-approval process and able to independently evaluate the validity of their claims. Given the sophistication of the audience to whom the off-label uses were promoted, this Court cannot conclude . . . that Defendants' speech was inherently misleading.").

379. *See* Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 86 (D.D.C. 1999).

380. *Id.*

381. *Caputo*, 288 F. Supp. 2d at 921.

382. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011) (quoting Edenfield v. Fane, 507 U.S. 761, 775 (1993)).

383. *See* United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012).

in the hearings that led to the legislation. When the FDCA was substantially revised in 1962, the amendments addressed concerns that doctors could not adequately evaluate frequently misleading claims made by drug manufacturers.[384] This concern should be underscored when off-label promotion is considered, as off-label products have not been proven safe or effective for the intended use.

One reason that doctors are not the sophisticated audience that courts and patients imagine them to be is the unyielding pressure on their time. Practicing physicians rely on information from pharmaceutical representatives because they have little time to assess new products independently.[385] One author states that doctors "can examine only a tiny sliver of the findings and minutiae published in journals concerning just their own specialty, and most read only summaries of most articles that they hear about."[386] Dr. Jerome Groopman, author of *How Doctors Think*, explains that most doctors learn about new products from the pharmaceutical industry and that it is rare for doctors to read in depth about new drugs.[387] Another doctor explains that an expert in the field would not need the information that a drug representative provides; the doctor who needs information, however, is "hard-pressed to contextualize

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384. *See* Waxman, *supra* note 1, at 301–11. Waxman describes the difficulty that doctors have in assessing the information provided by drug companies:

> [I]t was impossible for physicians to ascertain which drugs were effective for their claimed uses because of the large number of drugs being introduced, misleading advertising, the absence of adequate effectiveness testing, the fact that the evidence, if there was any, was either unpublished or scattered through hundreds of medical journals, and the lack of time and training most physicians have to devote to the study of detailed clinical reports.

Id. at 303 (citing S. REP. NO. 87-1744, at 37 (1962)); *see also* Alan H. Kaplan, *Fifty Years of Drug Amendments Revisited: In Easy-To-Swallow Capsule Form*, 50 FOOD & DRUG L.J. 179, 185–86 (1995) (purporting that the amendments of 1962 addressed the false representation issue by mandating inclusion of information in advertisements and printed descriptions).

385. *See, e.g.*, Howard Brody, *The Company We Keep: Why Physicians Should Refuse To See Pharmaceutical Representatives*, 3 ANNALS FAM. MED. 82, 83–84 (2005); Melinda L. Randall et al., *Attitudes and Behaviors of Psychiatry Residents Toward Pharmaceutical Representatives Before and After an Educational Intervention*, 29 ACAD. PSYCHIATRY 33, 35–36 (2005).

386. Mossman & Steinberg, *supra* note 375, at 266, 316; *see also* David T. Burke et al., *Reading Habits of Practicing Physiatrists*, 81 AM J. PHYS. MED. & REHAB. 779, 779 (2002) (noting that "most physiatrists only scan the table of contents and read the most important abstracts").

387. *See* JEROME GROOPMAN, HOW DOCTORS THINK 221 (2007).

the information being presented, or even simply to distinguish true from false information."[388] Thus, courts should not assume that doctors have the time or the inclination to assess and verify information from pharmaceutical representatives.

The efforts of detailers, coupled with doctors' reliance on information from drug representatives, leads to changes in prescribing habits.[389] One study considered the impact of commercial channels, including advertisements and detailing as well as scientific sources of information, such as published reports of clinical trials and review articles.[390] The study examined doctors' habits and beliefs regarding the efficacy of drugs about which the messages in scientific sources were very different than in commercial sources.[391] In fact, the study reported that advertisements for one of the drugs studied was the primary source of misinformation about the drugs' efficacy.[392] The study concluded that physicians were more influenced by commercial than scientific sources, but they were either unaware or unwilling to report that they were so influenced.[393] Detailing and salesmanship play dominant roles in physicians' choices about treatment.[394] Reports by the American Association of

388. *See* Steinman & Schillinger, *supra* note 368, at 22.

389. While detailing may be the most common type of off-label promotion, the practice may be one part of a more extensive off-label marketing strategy. Companies may use a combination of tactics to promote off-label uses. In combination, these tactics give the appearance to physicians that the off-label use has been accepted or gained traction in the medical community. Creating physician advisory boards and convincing prominent physicians to serve as "thought leaders" to influence colleagues to use a product off-label are tactics that physicians may not recognize as commercially influenced. Drug companies have also hired communication companies that get articles published in medical journals. *See supra* text accompanying notes 38–47 (discussing the *Neurontin* case); *see also* Sergio Sismondo, *Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry?*, PLOS MED. 1431 (Sept. 25, 2007), http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.prmed.0040286&representation=PDF (noting that "medical journals have real effects upon physician prescribing behavior, which is why pharmaceutical companies invest so much in their publication"). Even peer-reviewed, double-blind studies published in prestigious medical journals can spread faulty information when drug companies manipulate the results. *See* Richard Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, PLOS MED. 365 (May 17, 2005), http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.0020138& representation=PDF.

390. *See* Jerry Avorn et al., *Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 AM. J. MED. 4 (1982).

391. *See id.* at 4–6.

392. *See id.* at 5.

393. *See id.* at 6–7.

394. *See, e.g.*, Puneet Manchanda & Pradeep K. Chintagunta, *Responsiveness of Physician Prescription Behavior to Salesforce Effort: An Individual Level Analysis*, 15 MARKETING LETTERS 129, 138 (2004) (finding that pharmaceutical detailing impacts prescribing behavior); Natalie Mizik & Robert Jacobson, *Are Physicians "Easy*

Medical Colleges recognize that pharmaceutical marketing impacts the objective judgment of physicians to act in their patients' best interests.[395] Furthermore, studies conclude that the impact of marketing such as detailing creates a "net harm" to patients because doctors may be influenced to prescribe newer, more expensive drugs when a less expensive drug that may be more efficacious and safer is available; physicians may prescribe a drug when lifestyle changes or other nondrug therapies might be preferable; physicians may prescribe drugs when none are really required; and finally, the public trust may be tested by the perception of collusion between physicians and the pharmaceutical industry.[396]

Not surprisingly, most doctors believe they are immune from sales pitches by drug representatives.[397] One doctor stated, "You don't really think I would let a pizza lunch influence my decision-making process for my patients, do you?"[398] Doctors who believe that they are personally immune from commercial messages, however, believe their colleagues are influenced by commercial channels.[399]

With substantial evidence that detailers are trained to sell rather than to educate doctors, and that doctors do not have the time or the ability to distinguish truthful from misleading information provided by pharmaceutical representatives, the potential for harm is evident. The industry targets doctors who are likely to respond to overtures by changing their prescribing habits; the industry also selects the information about the product that is likely to produce a sale. The manufacturer has unique control over the information. The strategies of the pharmaceutical industry are not balanced by the physician's expertise and training. Rather, physicians unwittingly rely on the information provided without the time or resources to verify the information. Thus, the safeguards that the courts have assumed will protect consumers from misleading information do not exist.

Marks"?: Quantifying the Effects of Detailing and Sampling on New Prescriptions, 50 MGMT. SCI. 1704, 1714 (2004) (finding that past detailing affects current prescribing habits); Mossman & Steinberg, *supra* note 375, at 314–15; *see also* Manchanda & Honka, *supra* note 350, at 787 ("[D]etailing . . . affects physician prescription behavior in a positive and significant manner.").

395. *See, e.g.*, ASS'N OF AM. MED. COLLS., INDUSTRY FUNDING OF MEDICAL EDUCATION: REPORT OF AN AAMC TASK FORCE 6 (2008), *available at* https://members.aamc.org/eweb/upload/Industry%20Funding%20of%20Medical%20Education.pdf.

396. *See* Steinman & Schillinger, *supra* note 368, at 21–23.

397. ASS'N OF AM. MED. COLLS., *supra* note 376, at 7–8.

398. *Id.*

399. *See* GOLDACRE, *supra* note 282, at 274–75.

Although a blanket prohibition against off-label promotion would be more beneficial to the medical community and the safety of the public, pharmaceutical companies are likely to argue that even misleading information about off-label uses involves some truthful information. The Supreme Court has stated that when "truthful and nonmisleading expression will be snared along with fraudulent or deceptive commercial speech, the State must satisfy the remainder of the *Central Hudson* test by demonstrating that its restriction serves a substantial state interest and is designed in a reasonable way to accomplish that end."[400] Thus, there is the potential to bring even cases involving fraudulent and deceptive speech back into the morass of heightened or intermediate scrutiny.

V. HEIGHTENED SCRUTINY AND *CENTRAL HUDSON* ANALYSIS OF OFF-LABEL PROMOTION

The debate about off-label promotion and the First Amendment has come at a time when the Court seems intent on broadening protection for commercial speech or even eliminating the distinction between commercial and noncommercial speech.[401] It is unclear from the Court's discussion in *IMS Health* whether the Court is moving away from the *Central Hudson* analysis of commercial speech. The Court appears to offer two different standards for commercial speech. First, the traditional *Central Hudson* analysis, albeit with a more "unforgiving brand of intermediate scrutiny," and a second standard of "heightened scrutiny," which is unfamiliar in the commercial speech context.[402] Although these new methods of analysis make it more difficult to justify commercial speech, restrictions on off-label promotion should still withstand constitutional scrutiny.

Heightened scrutiny should not apply to restrictions on off-label promotion. In *IMS Health*, the Court stated that the "First Amendment

400. Edenfield v. Fane, 507 U.S. 761, 769 (1993).

401. Commercial speech received no protection until 1976. In *Valentine v. Chrestensen*, the Court held that the First Amendment does not protect commercial speech involving promoting a product for sale. 316 U.S. 52, 54 (1942). The Court overruled *Valentine* in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 760 (1976). The Court held that if it is lawful to sell a product, it must be lawful to inform consumers that the product is available to buy. *Id.* at 773. The Court developed protection of commercial speech in several cases. *See, e.g.*, Greater New Orleans Broadcasting Ass'n v. United States, 527 U.S. 173, 195–96 (1999); Rubin v. Coors Brewing Co., 514 U.S. 476, 491 (1995); Bolger v. Youngs Drug Prods. Corp., 463 U.S. 60, 76 (1983) (Rehnquist, J., concurring). For a history on the development of the commercial speech doctrine, see Kozinski & Banner, *supra* note 334.

402. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2679 (2011) (Breyer, J., dissenting) (advocating against the application of heightened scrutiny).

requires heightened scrutiny whenever the government creates 'a regulation of speech because of disagreement with the message it conveys.'"[403] In that case, the Court found that the purpose of the law was "viewpoint discriminatory."[404] Such analysis, however, does not hold up in the context of off-label promotion. Off-label promotion is prohibited not to further any favored point of view, but to insure that doctors and consumers receive accurate information. The premarket approval process insures that accuracy of information. Of course, the government seeks to enforce its premarket approval process and to discourage efforts to bypass it. To suggest that an agency seeking to uphold its own system is viewpoint discriminatory simply makes no sense. In *Caronia*, the court applied the heightened scrutiny test mechanically and conclusively, without any convincing analysis of why a prohibition on off-label promotion is viewpoint discriminatory.[405] The court merely concluded that the goal and impact of the restriction was to decrease off-label drug marketing.[406]

In his dissent in *IMS Health*, Justice Breyer pointed out that in highly regulated industries, such as the pharmaceutical industry, rules "necessarily draw distinctions on the basis of content" and are "speaker-based" because they apply to the regulated firms.[407] Breyer used off-label promotion as an example. According to Breyer, the FDA controls

> in detail just what a pharmaceutical firm can, and cannot, tell potential purchasers about its products. Such a firm, for example, could not suggest to a potential purchaser (say, a doctor) that he or she might put a pharmaceutical drug to an "off label" use, even if the manufacturer, in good faith and with considerable evidence, believes the drug will help. All the while, a third party (say, a researcher) is free to tell a doctor not use the drug for that purpose.[408]

Restrictions on off-label promotion should also survive *Central Hudson* analysis. Courts have readily acknowledged the government's interests in protecting the public health by insuring that drugs are safe

403. *Id.* at 2664 (quoting Ward v. Rock Against Racism, 491 U.S. 781, 791 (1989)).
404. *See id.* at 2663.
405. *See* United States v. Caronia, 703 F.3d 149, 164–65 (2d Cir. 2012).
406. *See id.* at 165.
407. *IMS Health*, 131 S. Ct. at 2677–78 (Breyer, J., dissenting).
408. *Id.* at 2678. In *IMS Health*, Breyer maintained that applying heightened scrutiny to commercial speech "opens a Pandora's Box of First Amendment challenges to many ordinary regulatory practices that may only incidentally affect a commercial message. . . . [I]t reawakens *Lochner*'s pre-New Deal threat of substituting judicial for democratic decisionmaking where ordinary economic regulation is at issue." *Id.* at 2685.

and effective.[409] Courts should also conclude that prohibiting off-label promotion directly advances that interest. In *Washington Legal Foundation v. Friedman*, for example, the court found that restricting off-label promotion is "one of the few mechanisms available to FDA to compel manufacturer behavior."[410] In *Caronia*, the court erroneously concluded that the restriction did not directly advance the government's interest because off-label use is lawful.[411] In doing so, the court did not give adequate consideration to the distinction between off-label prescribing and off-label promotion.[412] Off-label prescribing allows doctors to make scientifically sound medical decisions about individual patients,[413] giving them the option to prescribe off-label when patients need a treatment that is not yet available or not proven effective for the off-label use.[414] The FDA recognizes that off-label uses may be valuable and seeks to avoid intrusion on the discretionary decisions of healthcare professionals.[415] Off-label marketing encourages prescribing decisions based on unreliable and one-sided information that is scripted for pharmaceutical representatives in an effort to reach new lucrative markets without the time, money, and risks involved in the FDA approval process, and without reliable scientific knowledge about the safety or efficacy of the product for the use promoted. Thus, courts should not follow the reasoning in *Caronia* and should conclude that restricting off-label promotion directly advances the government's interesting in insuring that drugs are safe and effective.

Courts should also find that restrictions against off-label promotion meet the final prong of *Central Hudson* because there is a reasonable fit between the restrictions and the government's interests, and because

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409. *See, e.g.*, *Caronia*, 703 F.3d at 166 (quoting FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000) ("[O]ne of the [FDCA's] core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use.").

410. 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *vacated in part sub nom.* Washington Legal Found. v. Henney, 202 F.3d 331, 336–37 (D.C. Cir. 2000).

411. *See Caronia*, 703 F.3d at 166.

412. Even as doctors recognize the benefits of some off-label prescriptions, questions have increasingly arisen regarding the scientific rationale for some off-label uses. *See, e.g.*, Becky A. Briesacher et al., *The Quality of Antipsychotic Drug Prescribing in Nursing Homes*, 165 ARCHIVES INTERNAL MED. 1280, 1280 (2005) (more than one-fourth of nursing home residents received antipsychotic medications, many of which were off-label, exceeded dosage guidelines, or both).

413. *See* GROOPMAN, *supra* note 387, at 218.

414. *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, 971 (1999) (explaining that off-label prescribing is particularly important in certain specialties, such as cancer treatment and pediatric medicine).

415. *See* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).

there are no other reasonable alternatives. In *Caronia*, the court found that regulations prohibiting off-label promotion did not meet this test because they were not sufficiently narrowly drawn.[416] The court then proceeded to list several other methods the government might employ to better regulate off-label promotion.[417]

In suggesting alternative methods of regulating off-label, the court ignored the fact that restrictions on off-label promotion were crafted to address real abuses and that several of its suggestions had already been tried and proven ineffective. Representative Henry A. Waxman, who has consistently championed the need for restricting off-label promotion by pharmaceutical companies, explained that congressional documents and hearings have consistently demonstrated that disclaimers and postmarket actions do not work. In support of limiting promotion of unapproved drugs, Waxman wrote:

> There . . . was abundant evidence to support the conclusion that alternatives, such as disclaimers disclosing the state of the evidence supporting a claim, and postmarket enforcement actions, were inadequate to stop deceptive and dangerous products. The record revealed that when there is no requirement to conduct the tests necessary to establish safety and effectiveness, such tests rarely are conducted. Disclaimers cannot in any way address the grave harm to patients caused by a marketplace in which no one is sure which products work and which do not: many patients are denied effective treatment while others risk serious side effects without any benefit that would justify the risk.[418]

Postmarket enforcement takes months or even years, during which time a drug remains on the market, exposing patients to dangerous or ineffective treatment. Evidence shows that disclaimers have a limited impact on physicians, and that consumers frequently misinterpret or ignore them.[419]

VI. CONCLUSION

Although the government may face challenges in prosecuting pharmaceutical companies for off-label promotion, it should not be deterred by the Second Circuit's decision in *Caronia*. The government has at least two options in pursuing pharmaceutical companies for off-label promotion. First, emphasizing that a defendant is being prosecuted

416. United States v. Caronia, 703 F.3d 149, 167–68 (2d Cir. 2012).
417. *See id.* at 168; *supra* note 225.
418. Waxman, *supra* note 1, at 300.
419. *See* Kesselheim, *supra* note 28, at 250–51.

for his intent to misbrand rather than for promotion itself might be enough to withstand First Amendment scrutiny. Second, prosecutors should focus increasingly on the false or misleading nature of off-label promotion to take the legal analysis outside of the scope of the First Amendment. Furthermore, sound arguments distinguish the oral promotional statements by pharmaceutical representatives from the speech the U.S. Supreme Court found constitutionally protected in *Western States* and *IMS Health*. Prohibitions on off-label promotion are not subject to the heightened scrutiny standard the Court employed in *IMS Health* because the restrictions do not express any particular point of view; they merely seek to uphold the regulatory scheme that protects the public by requiring scientific testing of drugs for safety and efficacy. These restrictions easily satisfy the *Central Hudson* test because they directly advance the government's substantial interest in protecting the public health through the FDA's premarket approval process in a manner that is effective and no more restrictive than necessary.

Courts should be more sensitive to the fact that restrictions on off-label promotion were based on years of experience and evidence about the abuses and harms associated with off-label promotion. *Caronia* is but the latest in several attempts by the pharmaceutical industry to loosen restrictions on off-label promotion. The power of the industry to dismantle legislation designed to give the public accurate information and protect the public from misleading and biased information is disheartening. The government should continue to investigate and prosecute companies and individuals who strategically mislead doctors and the public into prescribing, purchasing, and using drugs that have not been scientifically proven safe and effective for a particular use.