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After Caronia: First Amendment Concerns in Off-Label Promotion

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by

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Abstract

The government has successfully prosecuted pharmaceutical companies for off-label promotion of drugs, maintaining that such promotion impermissibly undermines the FDA's pre-market approval process and jeopardizes the public health. In several recent cases, however, pharmaceutical companies have alleged that regulations prohibiting such promotion are unconstitutional because off-label promotion is protected under the First Amendment. Two recent Supreme Court cases contain language that gives broad protection to advertising and marketing in the pharmaceutical field. This paper questions the reach of these cases as applied to the practice of off-label promotion through detailing.

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 When the FDA approves a drug or device and its label, it does so for a particular indication.² Frequently, however, a physician may prescribe a drug or use a device that has been FDA-approved for one indication for a different indication. Such practices are not illegal, as the FDA does not

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¹ The FDA regulates the safety and efficacy of food, drugs, medical devices, and cosmetics. This paper focuses on its role in regulating the pharmaceutical 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) (2006). The FDA's authority to regulate drugs and medical devices is derived from several statutes. The Federal Food, Drug, and Cosmetic Act (FDCA) was passed in 1938 after a toxic elixir killed 107 people, including many children. 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. The FDA conducted a Drug Efficacy Implementation Study to review the efficacy of 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. 21 U.S.C. § § 351-360n. The MDA responded to findings that faulty medical devices have caused numerous injuries and deaths.

² When the FDA approves a new drug, the approval extends only 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). If the manufacturer seeks to introduce the drug into commerce for a new use, it must seek and obtain FDA approval for that new use. 21 U.S.C. § 355(a).

regulate the practice of medicine.³ If a physician prescribes a drug for a use or 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.”

Off-label prescribing by physicians is completely different from off-label marketing by pharmaceutical companies. While patients may trust the judgment of their physicians in making prescribing decisions about off-label use, the promotion of drugs for off-label use raises controversial questions.

The FDA discourages off-label promotion because the practice allows manufacturers to evade the kind of testing that allows 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 to human lives.”⁴ While companies maintain that the information they provide physicians is truthful, it is likely that they do not provide the *whole truth* and that information is frequently presented in a manner that is inherently fraudulent or misleading. 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 in 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.”⁵

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.”⁶ In fact, studies suggest that more than 20% of prescriptions are written for off-label uses.⁷ Pharmaceutical companies and their supporters emphasize the benefits of off-label prescribing and the need for off-label promotion. Advantages of off-label prescription include delivery of needed new treatments sooner, rather than at the end of a lengthy and costly approval process. Supporters also maintain that off-label promotion allows the company that has the most complete information about

³ The FDCA states: “Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.” 21 U.S.C. § 396.

⁴ Waxman, *supra* note 1.

⁵ Department of Justice, Press Release, Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Off-Label Promotion of Zyprexa (Jan. 15, 2009) <http://www.justice.gov/opa/pr/2009/January/09-civ-038.html> (last visited July 10, 2013). 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 treating unapproved uses such as dementia, Alzheimer’s dementia, depression, anxiety, sleep problems, as well as behavioral symptoms such as agitation, aggression and hostility. *Id.* 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.*

⁶ Mina Kimes, *Bad to the Bone: A medical horror story*, FORTUNE, <http://features.Blogs.fortune.cnn.com/2012/09/18/synthes-norian-criminal>.

⁷ See David C. Radley, et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCH. INTERNAL MED. 1021, 1023 (2006); see also Jane Henney, *Safeguarding Patient Welfare: Who’s in Charge?* 145 ANNALS INTERNAL MED. 305, 305 (Aug. 15, 2006), available at <http://www.annals.org.proxy.bc.edu/cgi/content/full/145/4/305>.

the product to give accurate, timely information to physicians.⁸ While off-label 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.⁹ The product, Norian XR, filled fractures and essentially became part of the bone. The manufacturer of the product sought to use it in other types of surgeries, such as vertical compression fractures of the spine (VCFs). 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. 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.¹⁰ The label approved by the FDA on the product cautioned against use in surgeries for VCF.

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. At least five people died of pulmonary clots shortly after the bone cement was injected during spine surgery. 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.¹¹ His partner, however, believed the product was safe and effective and continued to use it; he subsequently lost a patient during surgery.¹² Ultimately, use of the product for VCFs was halted.¹³ Both Synthes and Norian pled guilty to numerous misdemeanors and paid substantial fines. Four executives were charged as “responsible corporate officers.”¹⁴ They pleaded guilty to one misdemeanor count of shipping adulterated and misbranded Norian XR in interstate commerce and were sentenced to several months in jail.¹⁵

The outrageous facts of this case demonstrate the extreme harm that can result from off-label promotion of drugs.¹⁶ But the case illustrates several points that are critical to the debate about off-label promotion even in cases that are

⁸ 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 & ETHICS 299, 305-06 (2010).

⁹ Kimes, *supra* note 6.

¹⁰ 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. Tests of the product on pigs also showed that clots formed in the lungs. See Press Release, U. S. Department of Justice, Former Executives of International Medical Device Maker Sentenced to Prison in Unlawful Clinical Trials Case, (Nov. 21, 2011), <http://www.fda.gov/ICECI/CriminalInvestigations/ucm280937.htm>.

¹¹ Kimes, *supra* note 6.

¹² *Id.*

¹³ *Id.* Not only did the company continue to market the product until after the third death, but it failed to report details of the deaths to the FDA as required. See Press Release, U. S. Department of Justice, *supra* note 9.

¹⁴ See Press Release, U. S. Department of Justice, *supra* note 10.

¹⁵ *Id.*

¹⁶ 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*:

less tragic. First, the company was willing to overlook serious risks associated with its product in order to reach a large, lucrative market. Second, is the perception that because a drug is approved for one use, it must be safe for other uses. As the Norian case illustrates, a product can be safe and effective for some uses, and excessively risky for others. Third, the company chose to avoid the time-consuming and expensive FDA approval process to get its product to market quickly.¹⁷ Fourth, surgeons were led to believe the product was safe and were not fully informed of the risks associated with the product. Fifth, patients were unaware that they were the victims of experimentation.

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 companies.¹⁸ 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.¹⁹

In response to an increase in government prosecution of cases involving off-label promotion, the industry has complained that such prosecutions are overly aggressive.²⁰ It is possible, however, and perhaps more likely, 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.²¹ Approved for use in conjunction with other drugs to treat epilepsy and for dosages ranging

Balancing Public Health Goals and Commercial Speech, 37 AM. J. L. AND MED. 225, 226 (2011) (detailing individual patient risks and risks to the health care system).

¹⁷ FDA approval of medical devices is governed by the Medical Device Amendments (MDA). 21 U.S.C. § 351-360n. 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 pre-market approval. *See id.* § 360j(g). The IDE is designed to “encourage . . . the discovery and development of useful devices . . . and maintain optimum freedom for scientific investigators.” *Id.* The manufacturer of Norian XR, however, opted not to seek an IDE. *See Kimes, supra* note 6 .

¹⁸ *See* discussion *infra* at Part IV.B.

¹⁹ *See id.*

²⁰ *See* Osborn, *supra* note 8, 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 Wikipedia, http://en.wikipedia.org/wiki/List_of_off-label_promotion_pharmaceutical_settlements (last visited August 29, 2013). Healthcare advocacy group Public Citizen reported that between Nov.2, 2010 and July 18, 2012, there were 74 civil and criminal judgments and settlements against pharmaceutical companies, totaling \$10.2 billion. Not all of the settlements involved unlawful promotion, although seven of the top ten did. *See* Eric Palmer, FiercePharma, 10 Largest Settlements and Judgments (Oct. 17, 2012) <http://www.fiercepharma.com/story/10-largest-settlements-and-judgments/2012-10-17>.

²¹ *See* United States ex rel. Franklin v. Parke-Davis, 147 F. Supp. 2d 39 (D. Mass. 2001). Pfizer acquired Warner Lambert, including its pharmaceutical division, Parke-Davis in 2000. Pfizer maintains that the activity in question took place before its acquisition. Each of the companies was named as a defendant in the suit. For a more detailed description of the issues involved in the case, see generally Stephanie Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN ST. L. REV. 41(2005). Pfizer paid \$430 million to settle the suit brought by the Department of Justice. 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 as migraines and bipolar disorder. 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 mg a day. *See* In re Neurontin Mktg. & Sales Practices Litig. (Kaiser Findings), No. 04-cv-10739-PBS, 2011 U.S. Dist. LEXIS 99593, 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

between 900 to 1800 mg per day, Parke-Davis marketed the drug for off-label uses including bipolar disorder, pain, and migraines, and for dosages up to 4800 mg per day, without any proof that the drug was safe or effective for these indications.²² Internal company documents revealed that one employee referred to Neurontin as “the ‘snakeoil’ of the twentieth century.”²³ The off-label marketing effort was referred to in Parke-Davis memos as a “strategic swerve” to increase profits from Neurontin.²⁴ 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 promoted as well as suppressing, spinning, or neutralizing negative studies.²⁵ The company also engaged in a “publication strategy” to promote the drug and hired doctors to talk about off-label uses.²⁶ 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. Taped voicemail messages indicate 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 coming off Neurontin before they’ve been up to at least 4,800 milligrams a day.²⁷

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 dollars.²⁸ Following the company’s off-label marketing strategy, which began in 1995, projections indicate that 90% of Neurontin prescriptions were for off-label uses and sales soared from \$97.5 million in 1995 to approximately \$2.7 billion in 2003.²⁹

the Court of Appeals for the First Circuit affirmed the judgment of the lower court. In *Re: Neurontin Marketing and Sales Practices Litigation*, 712 F.3d 21 (1st Cir. 2013). Numerous cases against Pfizer for the off-label promotion of Neurontin are ongoing.

²² See *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d at 48-49.

²³ *In re Neurontin Mktg. & Sales Practices Litig.*, 748 F. Supp. 2d 34 (D. Mass. 2010), amended and superseded by Kaiser Findings, 2011 WL 3852254.

²⁴ *In re Neurontin Mktg. & Sales Practices Litig.*, 748 F. Supp. 2d 34 (D. Mass. 2010), amended and superseded by Kaiser Findings, 2011 WL 3852254.

²⁵ See Stephanie Saul, *Experts Conclude Pfizer Manipulated Studies*, N.Y. TIMES, Oct. 8, 2008, available at <http://www.nytimes.com/2008/10/08/health/research/08drug.html/>.

²⁶ *In re Neurontin Mktg. & Sales Practices Litig.*, 748 F. Supp. 2d 34 (D. Mass. 2010), amended and superseded by Kaiser Findings, 2011 WL 3852254.

²⁷ Dateline: *Drug Giant Accused of False Claims* (NBC television broadcast, July 11, 2003) (transcript on file with author).

²⁸ *In re Neurontin Mktg. & Sales Practices Litig.*, 748 F. Supp. 2d 34 (D. Mass. 2010), amended and superseded by Kaiser Findings, 2011 WL 3852254.

²⁹ Julie Schmit, *Drugmaker Admitted Fraud, But Sales Flourish*, USATODAY.com, Aug. 16, 2004, http://usatoday30.usatoday.com/money/industries/health/drugs/2004-08-16-neurontin-cover_x.htm.

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.³⁰ Recently, however, several defendants have asserted that off-label promotion is speech protected by the First Amendment.³¹ Two cases in which the defendants asserted a First Amendment defense have reached the United States Courts of Appeal. In *United States v. Caronia*, the 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.³² In *United States v. Harkonen*, the 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.³³ 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, while the *Caronia* case focuses more broadly on off-label promotion as protected speech.

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).³⁴ 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.³⁵

³⁰ See Katherine A. Helm, *Protecting Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 19 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. § 1320a-7 (2005), individuals and entities may be excluded from participating in Medicare and State healthcare programs if convicted of healthcare fraud. The text of the provisions is available at the Legal Information Institute, Cornell University Law School, <http://www.law.cornell.edu/uscode/text/42/1320a-7>.

³¹ 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. The complaint maintained that the regulations criminalize manufacturer's speech even if it is truthful and non-misleading. See *Par Pharmaceutical, Inc. v. United States*, 11-cv-01820 (Oct. 14, 2011). Par's product, Megace ES is FDA-approved for the treatment of anorexia, cachexia, or unexplained, significant weight loss in patients diagnosed with AIDS. According to Par, the company sought to provide truthful, nonmisleading information about the on-label use of its drug Megace ES to doctors who might prescribe for off-label uses in treating wasting in cancer and geriatric patients. The company stated that a "manufacturer cannot be deemed to intend an off-label use merely because the manufacturer sells a drug with knowledge that physicians will prescribe the drug for an off-label use." Policy and Medicine, *Par Pharmaceuticals vs. FDA Calling for Truthful Speech vs. FDA Approved*, (Oct. 18, 2011) <http://www.policymed.com/2011/10/phar-pharmaceuticals-vs-fda>. Par dropped the suit as part of a settlement in which it agreed to plead guilty to a misdemeanor charge for misbranding the drug and paying criminal and civil fines. See *Pharmalot, Par Settles Off-Label Probe & Drops Free Speech Suit* (March 5, 2013), www.pharmalive.com/par-settles-label-probe-drops-free-speech-suit. Allergan, the manufacturer of Botox®, also challenged FDA restrictions on off-label promotion on First Amendment grounds. Allergan dropped its suit as part of its settlement with the government. Press Release, Department of Justice, *Allergan Agrees to Plead Guilty and Pay \$600 Million to Resolve Allegations of Off-Label Promotion of Botox®*, (Sept. 1, 2010), <http://www.justice.gov/opa/pr/2010/september/10-civ-988.html>.

³² 703 F. 3d 149 (2d Cir. 2012).

³³ No. 11-10209, No. 11-10242, 2013 U.S. App. LEXIS 4472 (9th Cir. March 4, 2013) (per curiam).

³⁴ See discussion *infra* at Part II.C.1.

³⁵ See *supra* note 31.

Detailing, the type of promotion at issue in *Caronia*, involves promoting drugs and devices to doctors in their offices. Detailing is especially important to off-label promotion because there is no prohibition against 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.³⁶

The argument that off-label promotion is protected by the First Amendment received a boost from two 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 that prohibited pharmacies from advertising that they compounded specific drugs violated the First Amendment.³⁷ In 2011, the Court held in *Sorrell v. IMS Health* that a Vermont statute that prohibited pharmaceutical companies from using prescriber-identifying information for marketing purposes violated the First Amendment.³⁸ Language in these decisions provided ammunition for challenging restrictions on off-label promotion by detailers. This paper questions the reach of the Supreme Court's decisions in *Western States* and *Sorrell* and whether the Second Circuit's reliance on these cases in *Caronia* is misplaced.

Part II of this paper 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 court's reasoning in *Caronia* and its reliance on the Supreme Court's decisions in *Thompson v. Western States Medical Center* and *Sorrell v. 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, nor that doctors are able to distinguish between misleading and non-misleading information. In Part V, the paper 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 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. The paper 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 *Sorrell* does not apply and the restrictions easily survive *Central Hudson* analysis. The paper concludes that the government should not be deterred from prosecuting companies and sales representatives who promote drugs for off-label uses.

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 sections provide background information for understanding the First Amendment challenges to off-label promotion.

A. What is Off-Label Promotion?

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

³⁷ 535 U.S. 357 (2002).

³⁸ 131 S. Ct. 2653 (2011).

Since 1962, the FDCA has required premarket approval of drugs for each indicated use before distribution in interstate commerce.³⁹ 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.”⁴⁰ If a company discovers new uses for a drug, new populations to treat, or new dosages, such uses must be approved by the FDA;⁴¹ otherwise, they are considered to be off-label. Because the FDA approval process is time-consuming and expensive,⁴² drug manufacturers may seek to bypass the approval process by marketing the drug off-label. 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.⁴³ 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. 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.⁴⁴ 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. GlaxoSmithKline settled the lawsuit.⁴⁵

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 prohibits introducing a drug into commerce without proper labeling about its indicated use, a practice referred to as misbranding.⁴⁶ 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.

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

³⁹ 21 U.S.C. § § 331(d), 355(a). For a history of FDA regulation in the drug industry see Helm, *supra* note 30, at 124-46.

⁴⁰ 21 U.S.C. § 355(d).

⁴¹ 21 U.S.C. § 321(p).

⁴² A New Drug Application to the FDA requires detailed reports of pre-clinical and clinical trials demonstrating safety and efficacy and the proposed labeling for the drug. 21 U.S.C. § 355(b). The requirements for an Investigational New Drug Application are set forth at 21 C.F.R. § 312.20. The various phases of an investigation, including initial volunteer studies, controlled clinical studies involving several hundred patients, and expanded and uncontrolled trials involving several hundreds to several thousands of patients are described in 21 C.F.R. § 312.21., *See generally* Julie C. Relihan, Note, *Expediting FDA Approval of AIDS Drugs: An International Approach*, 13 B.U. INT’L L.J. 229 (describing the drug approval process); *see also* FDA, How Drugs Are Developed and Approved, <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/> (last visited August 29, 2013).

⁴³ Press Release, Department 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 www.justice.gov/print/PrintOut3.jsp.

⁴⁴ *Id.*

⁴⁵ *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.*

⁴⁶ A drug is “misbranded” if the manufacturer alters the FDA-approved labeling to include any false or misleading statement. 21 U.S.C. § 352(a).

practice referred to as detailing. 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.⁴⁷ Thus, the restrictions that apply to pharmaceutical companies about 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. 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. The following sections summarize the rules and regulations as well as the case law relevant to off-label promotion.

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.⁴⁸ The Act also prohibits the "introduction or delivery for introduction into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded."⁴⁹ 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.⁵⁰ A prohibition on the misbranding of drugs pre-dates 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.⁵¹

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.⁵² Thus, when a pharmaceutical sales representative promotes a drug for off-label use, it is clear that the information he provides 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 the drug" as evidenced by the "labeling claims, advertising matter, or oral or written statements by such persons or their representatives."⁵³ Thus, when a pharmaceutical representative visits a doctor in his office and provides information about off-label uses, it is logical to conclude that his 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 the doctor's off-label prescription is legal, the pharmaceutical company and its representatives

⁴⁷ 21 U.S.C. § 396 (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, "Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling." PHYSICIANS DESK REFERENCE 2008, Forward (62nd ed. 2007). The United States 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).

⁴⁸ 21 U.S.C. § 355(a).

⁴⁹ 21 U.S.C. § 331(a).

⁵⁰ 21 U.S.C. § 352(f); 21 C.F.R. § 201.5.

⁵¹ See Helm *supra* note 30, at 125. The Pure Food and Drugs Act, ch. 3915, § § 1-13, 34 Stat. 768 (1906) was repealed in 1938. The text of the Act is available at the National Center for Biotechnology Information, <http://www.ncbi.nlm.nih.gov/books/NBK22116/>.

⁵² See 21 U.S.C. §321 (k), (m). 21 C.F.R. § 202.1. In *Kordel v. United States*, the Court held that a manufacturer can be found guilty of misbranding even though the product and the labeling information were shipped separately. 335 U.S. 345, 350 (1948).

⁵³ 21 C.F.R. § 201.128.

may be prosecuted for misbranding.⁵⁴ Pharmaceutical manufacturers and their representatives can face misdemeanor charges for misbranding or felony charges for fraudulent misbranding.⁵⁵

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 non-binding recommendations about how companies should respond to both private and public inquiries about off-label uses from health care professionals or consumers.⁵⁶ 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.⁵⁷ When consumers contact a company privately about off-label information, the company should respond privately with "truthful, non-misleading, accurate, and balanced" scientific information.⁵⁸ Responses should come from the company's medical affairs office, not its sales force and should be narrowly tailored to the inquiry.⁵⁹ 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.⁶⁰ When inquiries are posted on a public forum, the draft guidance recommends that a firm should respond in a non-promotional manner with contact information only about its own product.⁶¹ 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."⁶²

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 FDA Guidance, the agency issued nonbinding recommendations about the dissemination of off-label information in scientific or medical journals.⁶³ The agency states that if the recommendations are 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.⁶⁴ The recommendations emphasize that materials be peer-reviewed, independent of manufacturer funding, and not significantly influenced by a financial relationship with the manufacturer.⁶⁵ The information should also be based on "scientifically sound"

⁵⁴ See Jeffrey N. Wasserstein & Kurt R. Karst, *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.

⁵⁵ 21 U.S.C. § 333(a).

⁵⁶ FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-label Information about Prescription Drugs and Medical Devices (2011).

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² *Id.*

⁶³ 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), <http://www.fda.gov/oc/op/goodreprint.html>.

⁶⁴ *Id.*

⁶⁵ *Id.*

clinical investigations and not be false or misleading.⁶⁶ Recommendations also include that the materials be unabridged, accompanied by the approved labeling, and not attached to promotional materials.⁶⁷ The recommendations on disseminating printed materials about off-label use are substantially less burdensome than previous regulations. The FDA's revised thinking on this issue is largely due to successful litigation which challenged restrictions on First Amendment grounds.⁶⁸ This litigation is discussed in the following section.

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. The Supreme Court has not addressed off-label promotion through detailing, but cases decided by the Court expanding protection for commercial speech in general have provided fresh ammunition in the industry's battle for increased First Amendment protection. In response to First Amendment challenges, the government has indicated that it may be more selective in deciding which cases to prosecute.⁶⁹ The following section summarizes cases that addressed First Amendment challenges to off-label promotion as well as the Supreme Court cases that had a substantial impact on the Second Circuit's holding in *United States v. Caronia*.

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

Washington Legal Foundation, a public interest law and policy center, challenged the constitutionality of FDA Guidance that sought to restrict manufacturers' distribution of journal article reprints and textbooks to physicians if they contained information about off-label uses.⁷⁰ In general, the FDA Guidance stated that manufacturers should distribute materials referencing off-label uses only if the materials were unabridged and were primarily about approved FDA uses.⁷¹ The FDA sought to "strike the proper balance between the need for exchange of reliable scientific data and information within the health care community, and the statutory requirements that prohibit

⁶⁶ *Id.* Despite the FDA's new tolerance towards 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. AND MED. 203 (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).

⁶⁷ *Id.*

⁶⁸ 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), *order vacated as moot sub nom*, *Washington Legal Foundation v. Henney*, 202 F.3d 331, 336-37 (D.C. Cir. 2000). *But see* *Whitaker v. Thompson*, 353 F.3d 947 (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).

⁶⁹ See Defendants' Memorandum in Support of Motion to Dismiss, No. 1:11-cv-1820, *Par Pharmaceutical, Inc. v. United States*, (D.C. Jan. 11, 2012), at 27. ("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.")

⁷⁰ *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D. D.C. 1998).

⁷¹ *Id.* at 58 (citing 61 Fed. Reg. 52800 (1996)).

companies from promoting products for unapproved uses.⁷² 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. Among the requirements in the Guidance, the pharmaceutical industry objected most strenuously to the requirement that the primary focus of texts or reprinted articles distributed be about FDA-approved uses.⁷³

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 Supreme Court in *Bolger v. Youngs Drug Products Corporation*:⁷⁴ the speech is an advertisement; the speech refers to a specific product; and the speaker has an economic motive in disseminating the material.⁷⁵ 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 considerable financial resources to influence physicians and that they are more likely to disseminate only materials that favor their own product.⁷⁶

Having concluded that the speech in question was properly classified as commercial, the court applied the test announced by the Supreme Court in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.⁷⁷ *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.⁷⁸ The court concluded that the Guidance could not withstand constitutional scrutiny. The court rejected the FDA’s argument that off-label promotion is inherently misleading. The court stated that the “FDA exaggerates its overall place in the universe,”⁷⁹ by suggesting that information about uses not approved by the FDA is inherently misleading. 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.⁸⁰

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. It also found that these interests are 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. to control the labeling, advertising and

⁷² *Id.*

⁷³ *Id.* (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. at 52800 (1996)). 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. *Id.* The Guidance also required that medical textbooks and compendia provide a balanced presentation and that the text is not substantially prepared or edited by the manufacturer. *Id.*

⁷⁴ 463 U.S. 60 (1983).

⁷⁵ *Friedman*, 13 F. Supp. 2d at 64.

⁷⁶ *Id.* at 65 (citing 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 501 (1984)); *City of Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410, 426 ((1993)).

⁷⁷ 447 U.S. 557 (1980).

⁷⁸ *Id.* at 565.

⁷⁹ *Friedman*, 13 F. Supp. 2d at 67.

⁸⁰ *Id.*

marketing.”⁸¹ Nevertheless, the court found that the Guidance was more restrictive of speech than necessary.⁸² 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.⁸³ Because less restrictive means of meeting its interest were available, the court found, the government failed to meet *Central Hudson’s* requirements and violated the First Amendment. 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.⁸⁴

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.”⁸⁵ 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.”⁸⁶

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.⁸⁷ 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; to provide the materials to the FDA sixty days prior to dissemination; to disseminate materials in unabridged form; and to disclose to recipients that the materials pertain to an unapproved use of the drug.⁸⁸ 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.⁸⁹ The court was particularly concerned about the requirements for supplemental applications, stating “the supplemental application requirement of the act amounts to a kind of constitutional blackmail – comply with the statute or sacrifice your First Amendment rights.”⁹⁰

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.⁹¹ The FDA’s position led the United States Court of Appeals for the District of Columbia to declare the issue moot and to vacate the injunction of the lower court.⁹² The result of the litigation was that manufacturers were free to disseminate reliable scientific information

⁸¹ *Id.* at 72.

⁸² *Id.* at 73.

⁸³ *Id.*

⁸⁴ *Id.* at 74-75. The court also held that the FDA could not prohibit manufacturers from suggesting content to Continuing Medical Education providers. *Id.*

⁸⁵ *Id.* at 73.

⁸⁶ *Id.*

⁸⁷ The Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

⁸⁸ See 21 U.S.C. § 360(a).

⁸⁹ 56 F. Supp. 2d 81, 87 (D. D.C. 1999).

⁹⁰ *Id.*

⁹¹ *Washington Legal Foundation v. Henney*, 202 F.3d 331, 335 (D.C. Cir. 2000).

⁹² *Id.*

about off-label uses. In 2009, the FDA issued nonbinding recommendations about disseminating printed materials with information about off-label use.⁹³ The new recommendations are less burdensome to manufacturers.

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 United States Supreme Court in 2002. In *Thompson v. Western States Medical Center*,⁹⁴ the drug compounding industry complained that certain provisions of FDAMA unconstitutionally burdened protected speech. 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.⁹⁵ 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.⁹⁶

Drug compounding is a process that is designed to tailor medication to the needs of an individual patient.⁹⁷ 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 drugs.⁹⁸ Nevertheless, the FDA became concerned that compounding could provide a loophole for some

⁹³ See *supra* text accompanying notes 62-68.

⁹⁴ 535 U.S. 357, 360 (2002).

⁹⁵ *Id.* at 377.

⁹⁶ *Id.* at 369-73. See *supra* text accompanying notes 77-78, describing the *Central Hudson* test.

⁹⁷ *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 (citations omitted).

⁹⁸ *Western States*, 535 U.S. at 362. An outbreak of fungal meningitis associated with a product distributed by the New England Compounding Center (NECC) drew national attention to the compounding industry. A steroid injectable product received by approximately 14,000 patients across nineteen states caused at least thirty-two deaths and severe injuries to hundreds of patients. Following this tragedy, the role of federal regulators could be strengthened. See *The Fungal Meningitis Outbreak: Could It Have Been Prevented?* Before the H. Comm. on Energy and Commerce, Subcommittee on Oversight and Investigations, 112th Cong. (2012) (statement of Margaret A. Hamburg, M.D., Commissioner, Food and Drug Administration). The Commissioner of the FDA refers to court challenges to Section 503A of FDAMA, which restricted advertising or promotion of compounding drugs. She stated that the FDA "look[s] forward to working with Congress" in addressing issues regarding the FDA's authority over compounding pharmacies. *Id.* Congressman Edward J. Markey of Massachusetts, recently elected to the United States Senate, proposed legislation that would increase federal regulation for pharmacies that operate as drug manufacturers but would preserve state regulation over traditional small compounding agencies. The proposed legislation also would give the FDA authority to inspect certain compounding pharmacies. See *Verifying Authority and Legality in Drug (VALID) Compounding Act*, H.R. 2186, 112th Cong. (2013). The bill was assigned to the House Energy and Commerce Committee on May 23, 2013 and a hearing on "Reforming the Drug Compounding Regulatory Framework," was scheduled before the Subcommittee on Health on July 16, 2013. <http://democrats.energycommerce.house.gov/index.php?q=schedule>.

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*, N. ENGL. J. MED. 2012, 367: 1969-72 (Nov. 22, 2012), available at www.nejm.org/doi/full/10.1056/NEJMp1212667. 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.* The FDA's Compliance

pharmacists to manufacture and sell drugs “under the guise of compounding.”⁹⁹ Moreover, the government maintained that advertising is “a fair proxy for actual or intended large-scale manufacturing.”¹⁰⁰ 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.¹⁰¹ The regulations allowed compounders to advertise their services in general, but prohibited them from advertising the compounding of specific drugs.¹⁰² Pharmacies that specialized in compounding drugs challenged these provisions.¹⁰³

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. 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 which protects the public health; allowing compounded drugs to be available to those patients who need them; and balancing these competing interests.¹⁰⁴ 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.¹⁰⁵ 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.¹⁰⁶ The Court suggested several less burdensome alternatives

Policy Guide of 2002 contains many of the restrictions on compounding that appeared in Section 503A of FDAMA , but did not contain the restrictions on advertising. *See id.*

⁹⁹ *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.

¹⁰⁰ *Western States*, 535 U.S. at 371.

¹⁰¹ 21 U.S.C. §353a.

¹⁰² *Id.*

¹⁰³ *Western States*, 535 U.S. at 360.

¹⁰⁴ *Id.* at 368.

¹⁰⁵ *Id.* at 371.

¹⁰⁶ *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 balanced” between the risks and benefits associated with compounded drug prescriptions. *Id.* at 380-81 (citing Brief for Appellants in No. 99-17424 (CA9), p.55). 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 387. According to the dissent, the government seeks to prevent “the adverse cumulative effects

that would be non-speech-related.¹⁰⁷ In short, the Court found that there was insufficient evidence that the restriction on advertising were “necessary” as opposed to “merely convenient” in promoting the government’s interests.¹⁰⁸

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 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 United States 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.¹⁰⁹

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.¹¹⁰ 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.¹¹¹ Because off-label use is legal, the defendants maintained, off-label promotion cannot be restricted.¹¹²

The Seventh Circuit did not have to reach the First Amendment issue because, it concluded, selling the device was not lawful.¹¹³ 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.¹¹⁴ 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 manufacturer, which after all will have the best information?”¹¹⁵ The court stated that the Supreme Court’s analysis in *Western States* indicated that prohibiting manufacturers from “alerting consumers to

of multiple individual decisions” which could in the aggregate “undermine the safety testing system, thereby producing overall a net balance of harm.” *Id.* (citations omitted).

¹⁰⁷ *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 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 at wholesale to other state licensed persons or commercial entities for resale;”
- Limit the amount of compounded drugs that a pharmacy could sell out of state.

Id.

¹⁰⁸ *Id.* at 373.

¹⁰⁹ 517 F.3d 935, 940 (7th Cir. 2008).

¹¹⁰ *Id.* at 937.

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.* at 940.

¹¹⁴ *Id.* at 939.

¹¹⁵ *Id.*

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.”¹¹⁶

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.¹¹⁷ 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.”¹¹⁸ 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.¹¹⁹ 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.¹²⁰

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

In deciding a 2011 case, the United States Supreme Court made a strong statement about protecting the speech of pharmaceutical manufacturers.¹²¹ The case involved the Vermont Prescription Confidentiality Law, which prohibited pharmaceutical companies and similar entities from using prescriber-identifying information for marketing purposes. 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.”¹²² Significantly, the Court found that such speech is subject to “heightened scrutiny” rather than the intermediate scrutiny applied to commercial speech under the *Central Hudson* analysis.¹²³

Data miners and pharmaceutical manufacturers of brand name drugs challenged the Vermont law. Pharmacies are required by law to collect and maintain detailed files about each prescription filled.¹²⁴ 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.¹²⁵ The information is valuable to companies in effectively targeting doctors who might be inclined to change their prescribing habits. 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.¹²⁶ The Vermont legislature had concluded that the information that pharmaceutical marketers provide to doctors is “incomplete and biased.”¹²⁷ Moreover, the

¹¹⁶ *Id.*

¹¹⁷ *Id.* at 940.

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 940-41.

¹²⁰ *Id.* at 941.

¹²¹ *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

¹²² *Id.* at 2659.

¹²³ *Id.*

¹²⁴ *Id.* at 2660.

¹²⁵ *Id.*

¹²⁶ *Id.*

¹²⁷ *Id.* at 2661.

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.¹²⁸ 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.¹²⁹

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.¹³⁰ The Court found that the Vermont Law disfavored speech with a particular content (marketing) when expressed by certain disfavored speakers (pharmaceutical manufacturers).¹³¹ 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.¹³² Heightened scrutiny is required, the Court stated, "whenever the government creates 'a regulation of speech because of disagreement with the message it conveys.'"¹³³

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.¹³⁴ 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.¹³⁵ The Court found that the law does not advance Vermont's purported interests in protecting patient privacy and preventing influence on doctors' prescribing habits in a direct manner, as required.¹³⁶ 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.¹³⁷ The Court also rejected the state's argument that the law interferes with the doctor-patient relationship by influencing prescribing decisions.¹³⁸ The Court concluded that the fact that doctors find such speech persuasive does not remove it from First Amendment protection.¹³⁹ As in *Western States*,

¹²⁸ *Id.*

¹²⁹ *Id.* at 2659.

¹³⁰ Justice Breyer, dissented, joined by Justices Ginsburg and Kagan. 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*. *Id.* at 2673-84 (Breyer, J., dissenting). Justice Breyer was particularly concerned that applying a "heightened" First Amendment standard of review whenever . . . a [regulatory] program burdens speech would transfer from legislature 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 Brothers & Elliott, Inc.*, 521 U.S. 457, 476(1997)).

¹³¹ *Id.* at 2663.

¹³² *Id.* at 2663-64.

¹³³ *Id.* at 2664 (citing *Ward v. Rock Against Racism*, 491 U.S. 781, 791 (1989)).

¹³⁴ *Id.* at 2667-72.

¹³⁵ *Id.* at 2667 (citing *Central Hudson*, 447 U.S. 557, 566 (1980)).

¹³⁶ *Id.* at 2670.

¹³⁷ *Id.* at 2668.

¹³⁸ *Id.* at 2670.

¹³⁹ *Id.*

the Court emphasized the fact that the government cannot suppress information out of fear that the public will misuse that information.¹⁴⁰ Furthermore, the Court noted that doctors, as the recipients of information through detailing are “‘sophisticated, experienced’ consumers.”¹⁴¹ The Court noted that a 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.¹⁴²

As the cases from *Washington Legal Foundation* to *Sorrell* 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 thinking on the dissemination of printed materials. Language in Supreme Court decisions such as *Western States* and *Sorrell* encouraged the industry to expand First Amendment protection for off-label promotion by sales representatives. Neither of the Supreme Court cases, however, specifically addressed issues raised by off-label promotion through detailing. Furthermore, lower courts that considered the implications of off-label promotion through detailing expressed reservations and caution.

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.¹⁴³ Orphan, the manufacturer of the drug, agreed to pay \$20 million in penalties and victim compensation to resolve parallel criminal and civil investigations.¹⁴⁴ The plea agreement included a guilty plea by Orphan to one count of felony misbranding of a drug product for off-label uses under the FDCA.¹⁴⁵ Peter Gleason, a psychiatrist who the government alleged was paid tens of thousands of dollars to illegally promote Xyrem also pleaded guilty to a misdemeanor to conspire with Orphan Medical.¹⁴⁶ Dr. Gleason was sentenced to one year probation and a \$25 fine.¹⁴⁷ Alfred Caronia, however,

¹⁴⁰ *Id.* at 2671 (citing *Western States*, 535 U.S. at 374; *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 769-770 (1976)).

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ Orphan Medical was acquired by Jazz Pharmaceuticals in 2005. The 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. Press Release, United States Attorney’s Office, Eastern District of New York, Jazz Pharmaceuticals, Inc. Agrees To Pay \$20 Million To Resolve Criminal and Civil Allegations in “Off-Label” Marketing Investigation (July 13, 2007), www.justice.gov/usao/nye/pr/2007.2007jul13a.html.

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ Press Release, United States Attorney’s Office, Eastern District of New York, 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), www.justice.gov/usao/nye/pr/2006/2006apr05.html.

¹⁴⁷ See Harvey Silverglate, *A Doctor’s Posthumous Vindication*, WALL ST. J. (Dec. 25, 2012), <http://online.wsj.com/article/SB10001424127887323981504578174973015235686.html>. Silverglate writes that the decision by the Court of Appeals for the Second Circuit vindicated Gleason when Caronia “won the point” that Gleason had argued: “The 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

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.

A. The District Court Found that Prohibitions on Off-Label Promotion Withstand 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.¹⁴⁸ 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.

The drug that Caronia allegedly misbranded, Xyrem, is a powerful sleep-inducing depressant that was approved by the FDA for two indications: cataplexy, a condition associated with narcolepsy, and excessive daytime sleepiness associated with narcolepsy.¹⁴⁹ 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.¹⁵⁰ Designated as a Schedule III Controlled Substance for medical use, Xyrem cannot be sold or distributed to anyone other than for a prescribed use.¹⁵¹

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.¹⁵² Despite the serious risks associated with Xyrem, Caronia stated that it was "a very safe drug," with no contraindications.¹⁵³ 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.¹⁵⁴

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 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.¹⁵⁵ Having concluded that Caronia's promotion of the drug qualified as commercial speech, the court employed the *Central Hudson* test to assess its constitutionality.¹⁵⁶ *Central Hudson* requires: (1) that the speech is lawful and not misleading; (2) that the government demonstrate a substantial interest;

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.*

¹⁴⁸ United States v. Caronia, 576 F. Supp. 2d 385, 389 (E.D.N.Y. 2008).

¹⁴⁹ *Id.* at 388-89.

¹⁵⁰ *Id.* at 389.

¹⁵¹ *Id.*

¹⁵² *Id.*

¹⁵³ See United States v. Caronia, 703 F.3d 149, 172 n.3 (Livingston, J., dissenting).

¹⁵⁴ See *id.*

¹⁵⁵ Caronia, 576 F. Supp. 2d at 396 (citing *Bolger*, 463 U.S. 60, 66-68 (1983)).

¹⁵⁶ *Id.* at 396-402 (applying the test established in *Central Hudson Gas v. Public Service Commission of New York*, 447 U.S. 557 (1980)).

(3) that the regulation directly advances that interest; and (4) that the restriction is not more extensive than necessary.¹⁵⁷

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 pre-market approval process.¹⁵⁸ The court found that restrictions on off-label promotion by manufacturers directly advance the FDA's interest in maintaining its approval process.¹⁵⁹ Citing *Friedman* and *Caputo*, the court recognized that manufacturers 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.¹⁶⁰

Finally, the court found that the FDA restrictions on off-label promotion are not more restrictive than necessary. 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."¹⁶¹

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

The 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.¹⁶² In a 2-1 decision, the court stated that the government improperly construed the misbranding provision of the FDCA to prohibit promotional speech.¹⁶³

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.¹⁶⁴ Although the government argued that it emphasized promotion only as evidence of intent to misbrand, the court was not persuaded.¹⁶⁵ Instead, the court found the trial record showed that the defendant was prosecuted and convicted for his speech.¹⁶⁶ 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.¹⁶⁷ According to the Second Circuit, construing the FDCA's misbranding provisions to criminalize

¹⁵⁷ *Central Hudson*, 447 U.S. 557, 565 (1980).

¹⁵⁸ *Caronia*, 576 F. Supp. 2d at 398.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.* (referencing *Friedman*, 13 F. Supp. 2d at 72 and *Caputo*, 288 F. Supp. 2d at 921).

¹⁶¹ *Id.* at 401 (citing *Friedman*, 13 F. Supp. 2d at 72).

¹⁶² *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

¹⁶³ *Id.* at 168-69.

¹⁶⁴ *Id.* at 154.

¹⁶⁵ *Id.* at 160-62.

¹⁶⁶ *Id.* at 161.

¹⁶⁷ *Id.*

the simple promotion of a drug's off-label use by pharmaceutical representatives would "run afoul of the First Amendment."¹⁶⁸

When the Second Circuit heard the appeal in *United States v. Caronia*, it had the benefit of the Supreme Court's decision in *Sorrell v. IMS Health*,¹⁶⁹ which had not been decided when the district court reached its decision. The Court's statement in *Sorrell* 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.¹⁷⁰

In *Sorrell*, the Court required heightened scrutiny because the statute imposed both content and speaker based restrictions, restrictions which the Court stated are "presumptively invalid."¹⁷¹ 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).¹⁷² 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.¹⁷³

Following the Supreme Court's analysis in *Sorrell*, the Second Circuit also demonstrated that restrictions on off-label promotion cannot 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.¹⁷⁴ 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 FDA's approval process anticipates that drugs will be used off-label.¹⁷⁵ Moreover, drawing on *Sorrell*, the court found that prohibiting off-label promotion "paternalistically" interferes with both doctors' and patients' access to information about off-label use.¹⁷⁶ 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."¹⁷⁷ 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.¹⁷⁸

¹⁶⁸ *Id.* at 162.

¹⁶⁹ 131 S. Ct. 2653 (2011).

¹⁷⁰ *Id.* at 2659.

¹⁷¹ *Id.* at 2662-65.

¹⁷² *Caronia*, 703 F.3d at 165.

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 166.

¹⁷⁵ *Id.*

¹⁷⁶ *Id.*

¹⁷⁷ *Id.* at 167.

¹⁷⁸ *Id.* at 167-69. 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.

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.¹⁷⁹ 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.¹⁸⁰

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

The majority in *Caronia* suggests that a case in which off-label promotion is presented merely as evidence of the intent to misbrand could be successful.¹⁸¹ At the same time the court's analysis of the First Amendment challenge threatens to eviscerate the prohibition against misbranding – a prohibition which strikes at the very heart of the FDA's fundamental purpose. In a dissenting opinion, Judge Livingston makes convincing arguments that *Sorrell* and *Western States* do not compel the result reached by the majority and that restrictions on off-label promotion are constitutional.

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.¹⁸² Livingston cited the 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.”¹⁸³ She also cited a case decided by the Court of Appeals for the D.C. Circuit which concluded that using speech “in the form of labeling” to infer intent is constitutionally permissible.¹⁸⁴ In that case, *Whitaker v. Thompson*, the Court of Appeals for the District of Columbia 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.¹⁸⁵ The court found that the statements about the product's intended use were drug claims, subject to the FDA approval process and

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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 (medical malpractice and negligence theories of liability).
 7. Prohibit off-label prescription all together where such use is exceptionally concerning, as was done with human growth hormone.

¹⁷⁹ *Id.* at 160.

¹⁸⁰ *Id.*

¹⁸¹ *Id.* at 172.

¹⁸² *Caronia*, 703 F.3d at 169 (Livingston, J., dissenting).

¹⁸³ *Id.* at 171-72 (citing *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)).

¹⁸⁴ *Id.* at 176 (citing *Whitaker v. Thompson*, 353 F. 3d 947, 953 (D.C. Cir. 2004). The case involved sale of saw palmetto, an extract from a dwarf American palm, and what types of claims the seller could make on its label. The seller proposed a label which 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.

¹⁸⁵ 353 F.3d 947, 952 (D.C. Cir. 2004).

consequently that the proposed label constituted speech about unlawful activity.¹⁸⁶ The court found that “a product’s label may often be the only readily available evidence of the product’s intended use.”¹⁸⁷ In *Whitaker*, the court concluded that it is constitutionally 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 would be illegal.¹⁸⁸ 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 MS, were merely evidence of the intended uses and did not interfere with Caronia’s First Amendment rights.¹⁸⁹

Judge Livingston expressed concern as to whether the majority’s reasoning would ever allow a conviction for misbranding.¹⁹⁰ 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.¹⁹¹ In other words, “promotion of a use may demonstrate an objective intent that the drug be used for that purpose.”¹⁹² 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.”¹⁹³ 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 be legally consumed.¹⁹⁴

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

Judge Livingston was not persuaded that the Supreme Court’s decisions in *Western States* and *Sorrell* dictated the outcome in *Caronia*. She found that the cases are distinguishable because in *Western States* and *Sorrell* “[s]peech alone was sufficient to trigger punishment under the challenged statutes.”¹⁹⁵ The FDA regulation challenged in *Western States* prohibited pharmacies from advertising or promoting the compounding of a particular drug.¹⁹⁶ In *Sorrell*, the statute targeted speech directly because it prohibited pharmaceutical manufacturers from using

¹⁸⁶ *Id.* at 953.

¹⁸⁷ *Id.* at 952-53.

¹⁸⁸ *Id.* at 953.

¹⁸⁹ *Caronia*, 703 F.3d at 171-72 (Livingston, J., dissenting).

¹⁹⁰ *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.

¹⁹¹ *Id.* at 172-73.

¹⁹² *Id.* at 174.

¹⁹³ *Id.* at 175.

¹⁹⁴ *Id.* (referring to *Arsenic and Old Lace* (Warner Bros. Pictures 1944)).

¹⁹⁵ *Caronia*, 703 F. 3d at 176.

¹⁹⁶ *Western States*, 535 U.S. at 370-71.

prescriber identifiable information for marketing or promotion.¹⁹⁷ In contrast, something more than speech is required for conviction under the statute prohibiting misbranding. 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.”¹⁹⁸

Judge Livingston also demonstrated that the FDCA’s misbranding provisions can be distinguished from the content and speaker based scrutiny required by the Court in *Sorrell*. The dissent noted that *Sorrell* reaffirms the principle that restrictions on commercial speech may be constitutionally permissible because of the government’s interest in protecting consumers from harm.¹⁹⁹ Regarding the content-based restrictions, the statute challenged in *Sorrell* 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.²⁰⁰ The heightened scrutiny for speaker based restrictions used in *Sorrell* 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.”²⁰¹

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.²⁰² Judge Livingston noted that the government’s substantial interest in “preserving the effectiveness and integrity” of the FDCA’s new drug approval process is not disputed.²⁰³ 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.”²⁰⁴ 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.”²⁰⁵ 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.”²⁰⁶ 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.”²⁰⁷

¹⁹⁷ *Sorrell*, 131 S. Ct. at 2671.

¹⁹⁸ *Caronia*, 703 F. 3d at 176.

¹⁹⁹ *Id.* at 180 (citing *Sorrell*, 131 S. Ct. at 2672).

²⁰⁰ *Id.*

²⁰¹ *Id.* at 179.

²⁰² *Caronia*, 703 F.3d at 177 (Livingston, J., dissenting).

²⁰³ *Id.* at 178 (citing *Western States*, 535 U.S. at 369). In *Western States*, 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.

²⁰⁴ *Caronia*, 703 F.3d at 178 (citing *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000)).

²⁰⁵ *Id.* at 169.

²⁰⁶ *Id.* at 178 (citing *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 72 (D. D.C. 1998)), *vacated in part*, *Washington Legal Foundation v. Henney*, 202 F. 3d 331 (D.C. Cir. 2000); *see also Caputo*, 517 F. 3d at .940

²⁰⁷ *Caronia*, 703 F.3d at 179.

Judge Livingston concluded that the restrictions on off-label promotion are not more extensive than necessary.²⁰⁸ In her dissent, she refuted each of the alternative regulations proposed by the majority as either ineffective or impractical.²⁰⁹ 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.²¹⁰

Judge Livingston's dissent more accurately reflects Congress's concerns about the importance of the FDA approval process than does the majority opinion. 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 the strong arguments against the majority's decision presented by Judge Livingston, 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 Supreme Court relied on in *Western States* and *Sorrell* must be revisited in order 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 would be 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. 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 . . ." ²¹¹ 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.

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

While the *Caronia* decision purports to protect truthful, off-label speech, the 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.²¹² The decisions by the Ninth and Second Circuits do not create a clear circuit split because they

²⁰⁸ *Id.* at 179-80.

²⁰⁹ See *supra* note 178, 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.

²¹⁰ *Id.* at 179-180.

²¹¹ *Caronia*, 703 F. 3d at 172 n.3.

²¹² 2013 U.S. App. LEXIS 4472 at *4.

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. The fraudulent nature of the speech, according to the Ninth Circuit, removed the case from First Amendment analysis. 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. Because it is unpublished, the *Harkonen* decision is limited to the facts of the case.

In 2004, the Department of Justice began an investigation into the off-label marketing of the drug Actimmune.²¹³ The drug was approved by the FDA to treat two rare diseases that afflict approximately 800 Americans.²¹⁴ 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.²¹⁵ There is no cure for IPF. Unless patients receive a lung transplant, they usually die within three to five years.²¹⁶ Between 2000 and 2003, most sales of Actimmune were for the off-label treatment of IPF and sales increased from \$11 million to \$141 million.²¹⁷

The off-label promotion of Actimmune for IPF was sparked by a paper published in 1999, in the *New England Journal of Medicine*.²¹⁸ 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.²¹⁹ 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.²²⁰ In a subset of patients with milder disease, however, the trial showed that there might be encouraging results.

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.²²¹ Although the protocol for a study can be changed after the study begins, a final protocol must be in place

²¹³ United States v. Harkonen, No. C 08-00164 MHP, 2009 U.S. Dist. LEXIS 47255 (N.D. Cal. June 4, 2009), at *2 (*Harkonen I*).

²¹⁴ *Id.* at *3. In 1990, Actimmune was approved to treat chronic granulomatous disease. In 2000, it was approved to treat severe, malignant osteopetrosis. Both indications are rare disorders that primarily affect children. *Id.*

²¹⁵ United States v. Harkonen, No. C 08-00164 MHP, 2010 U. S. Dist. LEXIS 75528 (N.D. Cal. July 27, 2010) (*Harkonen II*).

²¹⁶ See Andrew Pollack, Talking Up a Drug For This (And That), N.Y. TIMES, (Apr. 27, 2002), <http://www.nytimes.com/2003/04/27/business/talking-up-a-drug-for-this-and-that>.

²¹⁷ *Harkonen I*, 2009 U.S. Dist. LEXIS 47255 at *8. Anecdotal information from patients who used Actimmune for IPF are 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 \$6,000 a month for the drug. He believes that subsequent clinical trials indicated that 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.” Mike Henderson, Patient's View on Actimmune CEO Sentence, Good Promotional Practices (May 5, 2011), <http://goodpromotionalpractices.com/2011/05/05/what-about-the-patients/>.

²¹⁸ *Id.* at *4.

²¹⁹ *Id.*

²²⁰ *Id.* at *5.

²²¹ *Harkonen II*, 2010 U. S. Dist. LEXIS 75528 at *11.

before the data is made available to the researchers to prevent manipulation of the data.²²² The protocol for the IPF trial involved one primary endpoint – “progression-free survival time.”²²³ 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.²²⁴ The trial also had ten secondary endpoints, all of which it missed. If a primary endpoint fails, secondary endpoints are considered to be “hypothesis generating,” providing information to be tested in future trials.²²⁵ Nevertheless, InterMune focused on the data generated by secondary endpoints and subgroup analyses.²²⁶

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 in order to promote the drug for IPF.²²⁷ 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.”²²⁸ 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.”²²⁹ Before the press release was issued, Harkonen had been told by many sources that the trial missed its primary endpoint as well as all ten secondary endpoints. Harkonen was told that the subgroup analysis results focusing on mild to moderate IPF patients were “unreliable and inconclusive.”²³⁰ 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.’”²³¹

²²² *Id.*

²²³ *Id.* at *13.

²²⁴ *Id.* at *25-26.

²²⁵ *See id.* at *19-20. In *BAD PHARMA*, Ben Goldacre explains the danger of changing outcomes from trials by “switching the primary outcome,” as well as the problems involved in subgroup analyses. *BEN GOLDACRE, BAD PHARMA: HOW DRUG COMPANIES MISLEAD DOCTORS AND HARM PATIENTS 200-212 (2012)*.

²²⁶ *Harkonen II*, 2010 U. S. Dist. LEXIS 75528 at *26.

²²⁷ *Harkonen I*, 2009 U.S. Dist. LEXIS 47255 at *6.

²²⁷ *Id.*

²²⁹ *Harkonen II*, 2010 U. S. Dist. LEXIS 75528 at *28-29. 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 analysis, 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. at 29.

²³⁰ *Id.* at 38-39.

²³¹ *United States v. Harkonen*, No. 11-10209, No. 1-10242, 2013 U.S. App. LEXIS 4472, at *11-12 (9th Cir. 2013) (*Harkonen III*).

The press release was distributed to sales representatives with instructions on how to discuss it with doctors. The company also hired a marketing firm to explore how pulmonologists would react to the information.²³² Sales representatives, complete with incentive and bonus plans related to sales of Actimmune for IPF, were sent to detail pulmonologists.²³³

Harkonen was indicted for disseminating information regarding Actimmune for the treatment of IPF with the intent to defraud and mislead, causing Actimmune to be misbranded.²³⁴ He was convicted on a charge of wire fraud but found not guilty on the misbranding count.²³⁵ Harkonen appealed his conviction, arguing that the press release was speech protected by the First Amendment.²³⁶

The Ninth Circuit began with the proposition that the First Amendment does not protect fraudulent speech.²³⁷ In a recent case, the United States Supreme Court cited fraud as one of the long-recognized categories of content-based speech that may be restricted.²³⁸ 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.²³⁹ 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 clinical personnel from seeing the press release prior to publication.²⁴⁰ 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."²⁴¹ 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.²⁴²

Harkonen maintained that his statements were protected by the First Amendment because they involved scientific debate and were beyond the reach of the wire fraud statute.²⁴³ This argument rested on a 1902 Supreme Court decision, *American School of Magnetic Healing v. McAnnulty*, which held that "genuine debates over whether a

²³² *Id.* at*7.

²³³ *Id.*

²³⁴ *Id.*

²³⁵ *Harkonen II*, 2010 U. S. Dist. LEXIS 75528 at *1.

²³⁶ *Harkonen III*, 2013 U.S. App. LEXIS 4472.

²³⁷ *Id.* at *4 (citing *United States v. Alvarez*, 132 S.Ct. 2537, 2544 (2012)).

²³⁸ *United States v. Alvarez*, 132 S. Ct. 2537, 2544 (2012) (citing *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 771 (1976)). In *United States v. 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. *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.

²³⁹ *Harkonen III*, 2013 U.S. App. LEXIS 4472at *7-8.

²⁴⁰ *Id.* at *5-6.

²⁴¹ *Id.* at *6.

²⁴² *Id.* at *6-7.

²⁴³ *Id.* at *8.

given treatment caused a particular effect are outside the scope of the mail and wire fraud statutes.”²⁴⁴ The Ninth Circuit found that *McAnnulty* does not prohibit all prosecutions based on fraudulent statements about the efficacy of a drug.²⁴⁵ 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.”²⁴⁶ Harkonen also argued that “his statements were fraudulent only if they were universally considered objectively false.”²⁴⁷ 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, chicanery or overreaching.”²⁴⁸ Finally, the court rejected Harkonen’s argument that “he was engaging in genuine scientific debate,” concluding that “genuine debates of any sort are, by definition, not fraudulent.”²⁴⁹ 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.²⁵⁰

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.²⁵¹ The *Harkonen* case 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

²⁴⁴ 187 U.S. 94 (1902).

²⁴⁵ *Id.* at *9.

²⁴⁶ *Id.* at *8 (citing *Seven Cases 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,” as well as “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 right an owner has to “give his views regarding the effect of his drugs” and “false and fraudulent representations.” *Id.* at 417-18. 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 418. As in *Harkonen*, the Court emphasized the “actual intent to deceive.” *Id.* at 519.

²⁴⁷ *Harkonen III*, 2013 U.S. App. LEXIS 4472 at *8-9.

²⁴⁸ *Id.* (citing *Carpenter v. United States*, 484 U.S. 19, 27 (1987))

²⁴⁹ *Id.* at *9.

²⁵⁰ *Id.* at *10.

²⁵¹ 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. 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 Ausness, “*There’s Danger Here, Cherie!*” *Liability for the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*,” 73 BROOKLYN L. REV. 1253, 1262-64. The company promoted OxyContin for use every eight hours instead of the twelve hours approved by the FDA. The company paid \$19.5 million to states to settle a civil suit based on its alleged promotion of off-label use. It 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. The \$600 million the company paid in fines and civil penalties was about ninety percent of the profits it initially made from OxyContin sales. *Id.*

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 Amendment²⁵² 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.”²⁵³ The Court has gone further, stating that governments may “ban commercial expression that is fraudulent or deceptive without further justification.”²⁵⁴ 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.

In *Western States*, the Court stated, “[w]e 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.”²⁵⁵ But in *Western States*, *Sorrell* and *Caronia*, the government did not assert that the defendant’s speech was false or misleading. In *Sorrell*, 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.”²⁵⁶ The information at issue in both *Western States* and *Sorrell* involved factual information that was verifiable. In *Western States*, the information at issue involved advertising that a particular compounder made a particular product;²⁵⁷ in *Sorrell*, the information involved which drugs particular doctors prescribed.²⁵⁸ In *Caronia*, the government most 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. Given the uncertainty of the Supreme Court’s analysis of commercial speech – the “heightened scrutiny” introduced in *Sorrell*, as well as what one justice termed the “unforgiving” version of *Central Hudson* introduced in *Western States*, 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 would be to argue that 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.”²⁵⁹ 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 “outright fraud.”²⁶⁰ In *Ohralik*, the Court also noted that in-person solicitation presents unique regulatory

²⁵² *Virginia State Bd. of Pharmacy*, 425 U.S. at 771.

²⁵³ See, e.g., *Zauderer v. Office of Disciplinary Counsel of the Supreme Court of Ohio*, 471 U.S. 626, 638 (1985).

²⁵⁴ See, e.g., *Edenfield v. Fane*, 507 U.S. 761, 768 (1993) (citing *Central Hudson*, at 563-64; *In re R.M.J.*, 455 U.S. 191, 203 (1982); *Metromedia, Inc. v. San Diego*, 453 U.S. 490, 507 (1981) (plurality opinion).

²⁵⁵ *Western States*, 535 U.S. at 367.

²⁵⁶ *Sorrell*, 131 S. Ct. at 2672.

²⁵⁷ *Id.*

²⁵⁸ *Sorrell*, 131 S. Ct. at 2659.

²⁵⁹ GOLDACRE, *supra* note 225, at 246.

²⁶⁰ 436 U.S. 447, 464-65 (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 448. The Court had previously held that states could not prohibit truthful advertising about legal services because it

difficulties because it is “not visible or otherwise open to public scrutiny.”²⁶¹ Such solicitations, the Court stated, are “one-sided” and may encourage “uninformed decisionmaking.”²⁶² The Court concluded that rules prohibiting in-person solicitation by lawyers are “prophylactic measures whose objective is the prevention of harm before it occurs.”²⁶³

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.²⁶⁴ 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.²⁶⁵ While 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.²⁶⁶ Furthermore, prohibitions on off-label promotion seek to prevent harm before it occurs, by insuring that drugs are properly tested for safety and efficacy. While these factors should persuade courts of the dangers of off-label promotion and the necessity of restrictions, the Supreme Court, with the exception of the *Ohralik* decision, has been hostile to “prophylactic” rules.²⁶⁷ Moreover, in *Ohralik*, the Court emphasized the vulnerability of distressed potential clients.²⁶⁸ By contrast, courts have viewed doctors, the targets of detailing, as sophisticated customers.²⁶⁹ While there are meritorious arguments

impermissibly inhibited the free flow of commercial information under the First Amendment. *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.

²⁶¹ *Ohralik*, 436 U.S. at 466.

²⁶² *Id.* at 457.

²⁶³ *Id.* at 458-59.

²⁶⁴ *Caronia*, 703 F.3d at 167.

²⁶⁵ Michelle M. Mello, David M. Studdert, and Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, N. ENGL. J. MED. 350;15, NEJM.org (April 9, 2009), available at http://e.hsph.harvard.edu/faculty/michelle-mello/files/Off-label_PDF.pdf.

²⁶⁶ *See Va. State Bd. of Pharmacy*, 425 U.S. at 762.

²⁶⁷ In *Edenfield v. Fane*, 507 U.S. 761 (1993), the Court held that a state ban on personal solicitation by Certified Public Accountants was unconstitutional. *Id.* at 777. The Court did not find the risks associated with in-person solicitation by attorneys were present in cases involving CPAs. The Court stated that “[b]road 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.* at 777.

²⁶⁸ *Ohralik*, 436 U.S. at 460.

²⁶⁹ *See, e.g., Sorrell*, 131 S. Ct. at 2671.

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.²⁷⁰

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.”²⁷¹ The Court has also stated that “[r]egulations that suppress the truth are no less troubling because they target objectively verifiable information.”²⁷² 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 “[l]isteners 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 of a political candidate or the divine inspiration of a television evangelist.”²⁷³ Judge Kozinski stated:

much 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, and 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.²⁷⁴

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.²⁷⁵ Furthermore, Judge Kozinski’s presumption that “much scientific expression can easily be labeled true or false” 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 *Sorrell* is the Court’s concern for the free flow of information and an informed public. 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. While the Court’s decision in *Sorrell* 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.

²⁷⁰ See discussion *infra* at Part IV.B .

²⁷¹ *Zauderer*, 471 U.S. at 644.

²⁷² 44 *Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 502 (1984).

²⁷³ Alex Kozinski and Stuart Banner, *Who’s Afraid of Commercial Speech?*, 76 VA. L. REV. 627, 635 (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) (arguing that “communicators who offer misleading scientific opinions cannot invariably enjoy First amendment protection if those opinions cause recognized legal injuries.”).

²⁷⁴ Kozinski & Banner, *supra* note 273, at 636-37.

²⁷⁵ See discussion *supra* at text accompanying notes 243-50 .

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.²⁷⁶

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.

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."²⁷⁷ The court also stated that the public interest is furthered when information that can "save lives" is provided, including information about off-label use.²⁷⁸ The court's view of detailing suggests that pharmaceutical representatives are educators who provide truthful, non-misleading information to doctors and that the risks of influencing prescribing habits are few because physicians are "sophisticated and experienced customers."²⁷⁹ 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. In describing how detailing works, through the lens of sales representatives and physicians, the following sections demonstrate that off-label promotion is inherently misleading. Allowing off-label promotion guts the FDA's pre-marketing 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.²⁸⁰

1. How Detailers Mislead Doctors

In *Sorrell*, 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."²⁸¹ The Court refers to "brand-name drugs" and, presumably, to detailing for FDA-approved uses, that have been tested for safety and efficacy. This section examines information from doctors and sales representatives about the impact of detailing

²⁷⁶ Waxman, *supra* note 1, at 306-07.

²⁷⁷ *Caronia*, 703 F. 3d at 166.

²⁷⁸ *Id.* at 167.

²⁷⁹ *Id.* at 166 (citing *Sorrell*, 131 S. Ct. at 2670-72 ("[The] fear that physicians, sophisticated and experienced customers, would make bad decisions if given truthful information" cannot justify content-based burdens on speech.)) (citations omitted).

²⁸⁰ Aaron S. Kesselheim, Michelle M. Mello, David M. Studdert, *Strategies and Practices in Off-label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, PLoS Med 8(4): e1000431. Doi:10.137/journal.pmed.1000431 (2011).

²⁸¹ *Sorrell*, 131 S. Ct. at 2663.

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, non-misleading information to physicians to be highly problematic.²⁸² Dr. Kassirer asserts that “the notion that this is all for education is nonsense” and the fact that companies spend so much money on advertising is evidence of their intent to influence physicians.²⁸³ Several researchers have concluded that the pharmaceutical industry spends more money on marketing than on research and development.²⁸⁴ In 2000, pharmaceutical firms reportedly spent a total of \$8.5 billion on marketing, with most of the money financing physician-industry interactions.²⁸⁵ A 2008 report estimated that companies spend as much as \$57.5 billion on advertising, double what they spend on research.²⁸⁶ 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.²⁸⁷ In 2008, pharmaceutical companies reportedly spent \$12 billion on detailing to physicians and other health care professionals.²⁸⁸ 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.²⁸⁹

The industry’s faith in detailing is evident in the growth of the number of drug representatives in the United States.²⁹⁰ Between 1995 and 2005, the number of pharmaceutical sales representatives increased from 38,000 to

²⁸² See Marcus Baram, *Ex-Drug Sales Rep Tells All*, ABCNEWS.com, available at <http://abcnews.go.com/Health/Story?id=4438095&page=1> (last visited May 31, 2013).

²⁸³ See *id.*

²⁸⁴ 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 & ETHICS 785 (2005).

²⁸⁵ See Alice LaPlante, *Marketing Directly to Physicians Reaps Higher Returns for Drug Companies*, Stanford Graduate School of Business Marketing Research (Aug. 2006), <http://www.gsb.stanford.edu/news/research/mktgnarayananpharmaceuticals.shtml>.

²⁸⁶ Marc-Andre Gagnon & Joel Lexchin, *The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States*, 5 PLOS MED. E1 (2008). 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* (2008), <http://www.phrma.org/sites/default/files/159/marketing> and promotion facts 071108 final.pdf.

²⁸⁷ Manchanda & Honka, *supra* note 284, at 785 (citing Dick R. Wittink, *Analysis of ROI for Pharmaceutical Promotion* (ARPP) (2002)), http://www.rxpromoroi.org/arpp/media/arpp_handout_0927.pdf.

²⁸⁸ Congressional Budget Office, *Promotional Spending for Prescription Drugs* (2009), available at <http://www.cbo.gov/ftpdocs/105xx/doc10522/12-02-DrugPromotBrief.pdf>.

²⁸⁹ See LaPlante, *supra* note 285; see also Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?* 283 JAMA 373, 373 (2000).

²⁹⁰ 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:

100,000.²⁹¹ 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.²⁹² Researchers have summarized the value of detailers to doctors as follows:

The 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.²⁹³

Although the Court's decision in *Sorrell* suggests that it is not perturbed by the influence that detailing has on doctors' prescribing habits,²⁹⁴ 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.²⁹⁵ The company admitted that for eight years it had a sales force dedicated to marketing Depakote for off-label uses.²⁹⁶ The drug was FDA-approved for use with epileptic seizures, bipolar mania and migraines but was marketed to nursing homes to treat symptoms of dementia in elderly patients. There was no scientific evidence that the drug was effective in controlling dementia. 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. The company pleaded guilty and agreed to pay \$1.6 billion for misbranding the drug.²⁹⁷ 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.

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.

²⁹¹ See Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, PLoS Medicine 4(4): e150 (2007).

²⁹² *Id.*

²⁹³ *Id.*

²⁹⁴ In *Sorrell*, 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*, 131 S. Ct. at 266 .

²⁹⁵ See Department of Justice, Press Release, *Abbott Labs to Pay \$1.5 Billion to Resolve Criminal & Civil Investigations of Off-Label Promotion of Depakote* (May 7, 2012), available at www.justice.gov/opa/pr/2012/May/12-civ-585.html.

²⁹⁶ *Id.*

²⁹⁷ See Fugh-Berman & Ahari, *supra* note 291.

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.²⁹⁸ 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.²⁹⁹ Thus, while 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.³⁰⁰

Detailers are trained to target doctors most susceptible to marketing efforts and to develop a relationship with them.³⁰¹ To ensure detailers 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.³⁰² A former drug representative for Eli Lilly described drug representatives as “young and attractive” and “eloquent and convincing,” but lacking in “any significant scientific training.”³⁰³ 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.”³⁰⁴

Sales representatives are tasked with identifying doctors who are likely to change their prescribing habits and with finding ways to make them do so. They develop profiles of doctor that will help them create a social relationship to increase influence.³⁰⁵ Detailers may bestow free samples, invitations to speak at various events, dinners, and expense-paid trips to doctors who write large numbers of prescriptions.³⁰⁶ Even

²⁹⁸ See *Caronia*, 703 F. 3d at 166-67.

²⁹⁹ 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*, THE AM. J. OF BIOETHICS, 10:1, at 23 (2010); see also Shahram Ahari, Letter to Congress, Testimony before the Special Senate Committee on Aging (March 2008) available at <http://www.aging.senate.gov/events/hr190sa.pdf>. (explaining that drug reps were trained to downplay side effects of a drug); Marcus Baram, Ex-Drug Sales Rep Tells All, ABCNEWS.com, available at <http://abcnews.go.com/Health/Story?id=4438095&page=1> (last visited).

³⁰⁰ A related issue about manufacturers’ control of information is raised by Peter Doshi and Tom Jefferson 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. 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. 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.*

³⁰¹ See *id.*

³⁰² See *id.*

³⁰³ See Ahari, *supra* note 299. 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.*

³⁰⁴ *Id.*

³⁰⁵ GOLDACRE, *supra* note 225, at 277-79.

³⁰⁶ *Id.*

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, conscious or subconscious, to return a favor.³⁰⁷

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 talk up the merits of your treatment. They will offer gifts, lunches, and forge personal relationships that may be mutually beneficial later.³⁰⁸

Most people would assume, as the court did in *Caronia*, that doctors can readily distinguish sales pitches from reliable scientific data. The next section explores how doctors who 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.³⁰⁹ 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. The court stated, that "[t]he government, however benign its motivations, simply cannot justify a restriction of truthful non-misleading 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."³¹⁰ 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 their claims."³¹¹ In *Sorrell*, the Court referred to prescribing physicians as "'sophisticated experienced' consumers."³¹² In *Caronia*, the court echoed that language.³¹³

³⁰⁷ See Association of American Medical Colleges, The Scientific Basis of Influence and Reciprocity: A Symposium, Baylor College of Medicine (June 12, 2007), available at <https://members.aamc.org/eweb/upload/The%20Scientific%20Basis%20of%20Influence.pdf>; see also GOLDACRE, *supra* note 225, at 281 (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.") (citations omitted).

³⁰⁸ GOLDACRE, *supra* note 225, at 244.

³⁰⁹ See *Caputo*, 288 F. Supp. 2d at 921 ("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 as inherently misleading.").

³¹⁰ *Henney*, 56 F. Supp. at 86.

³¹¹ *Caputo*, 288 F. Supp. 2d at 921.

³¹² *Sorrell*, 131 S. Ct. at 2671.

The conclusions that courts have made about doctors' ability to discern valuable from misleading information is hard to understand as the reasons for current restrictions on promotion were extensively addressed 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."³¹⁴ 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.³¹⁵ 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."³¹⁶ 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.³¹⁷ 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 the information being presented, or even simply to distinguish true from false information."³¹⁸ 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.³¹⁹ One study considered the impact of commercial channels, including advertisements and

³¹³ *Caronia*, 703 F.3d 149, 166 (2d Cir. 2012).

³¹⁴ See Waxman *supra* note 1, at 301-08 (2003). Waxman describes the difficulty that doctors have in assessing the information provided by drug companies:

it 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 302 (citing DRUG INDUSTRY ACT OF 1962, S. REP. NO. 1744, 87th Cong., 2d Sess., pt. 1, at 37 (1962)); see also Alan H. Kaplan, *Fifty Years of Drug Amendments Revisited*, 50 FOOD & DRUG L.J. 179, 185-86 (1995).

³¹⁵ See, e.g., Howard Brody, *The Company We Keep: Why Physicians Should Refuse to See Pharmaceutical Representatives*, 3 ANNALS OF FAM. MED. 82, 83 (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).

³¹⁶ David T. Burke et al., *Reading Habits of Practicing Physiatriests*, 81 AM J. PHYS. MED. & REHABILITATION 779 (2002) ("most physiatriests only scan the table of contents and read the most important abstracts").

³¹⁷ JEROME GROOPMAN, *HOW DOCTORS THINK* 221 (2007).

³¹⁸ See Steinman & Schillinger, *supra* note 299, at 22.

³¹⁹ 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

detailing as well as scientific sources of information, such as published reports of clinical trials and review articles.³²⁰ The study examined doctors' habits and beliefs about the efficacy of drugs in which the message for a particular use was very different in the scientific sources than in the commercial sources.³²¹ In fact, the study reported that advertisements for one of the drugs studied was the primary source of "misinformation" about the drugs' efficacy.³²² 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.³²³ Detailing and salesmanship play dominant roles in physicians' choices about treatment.³²⁴ Reports by the American Association of Medical Colleges (AAMC) recognize that pharmaceutical marketing impacts the objective judgment of physicians to act in their patients' best interests.³²⁵ Furthermore, studies also 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 non-drug 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.³²⁶

traction in the medical community. Creating physician advisory boards, 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 the discussion of the Neurontin case *supra* at text accompanying notes 21-29; see Sergio Sismondo, *Ghost Management: How Much of the Medical Literature is Shaped Behind the Scenes by the Pharmaceutical Industry?* 4 PLoS MED e286 (2007) (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*, 2 PLoS MED. E138 (2005).

³²⁰ Jerry Avorn, M.D., Milton Chen, & Robert Hartley, M.D., *Scientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, THE AM. J. OF MED., Vol. 73, at 4 (July 1982).

³²¹ *Id.* at 4-6.

³²² *Id.* at 5.

³²³ *Id.* at 6-7.

³²⁴ 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 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); Douglas Mossman, MD & Jill L. Steinberg, *Promoting, Prescribing, and Pushing Pills: Understanding the Lessons of Antipsychotic Drug Litigation*, 13 MICH. ST. U. J. MED. & LAW, 263, 268 (2009); see also Manchanda & Honka, *supra* note 284, at 787 ("Detailing affects physician prescription behavior in a positive and significant manner.").

³²⁵ Association of American Medical Colleges, *Industry Funding of Medical Education: Report of an AAMC Task Force* (2008), available at http://services.aamc.org/publications/showfile.cfm?file=version114.pdf&prd_id=232.

³²⁶ See Steinman & Schillinger, *supra* note 299, at 21-23.

Not surprisingly, most doctors believe they are immune from sales pitches by drug representatives.³²⁷ One doctor stated, “You don’t really think I would let a pizza lunch influence my decision-making process for my patients, do you?”³²⁸ Doctors who believe that they are personally immune from commercial messages, however, believe their colleagues are influenced by commercial channels.³²⁹

With substantial evidence that detailers are trained to sell rather than to educate doctors and that doctors do not have the time to 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 habit and 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.

While 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.”³³⁰ 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.³³¹ It is unclear from the Court’s discussion in *Sorrell* whether the Court is moving away from the *Central Hudson* analysis of commercial speech. The Court appears to be offering two different standards for commercial speech. First, the traditional *Central Hudson* analysis, albeit with a more “unforgiving brand of intermediate scrutiny”³³² and a second standard of “heightened scrutiny” unfamiliar in the commercial speech

³²⁷ Association of American Medical Colleges, *The Scientific Basis of Influence and Reciprocity: A Symposium*, Washington, D.C., (2007).

³²⁸ *Id.*

³²⁹ GOLDACRE, *supra* note 225, at 275 (citations omitted).

³³⁰ *Edenfield*, 507 U.S. at 769 (citing *In re R.M.J.*, 455 U.S. at 203).

³³¹ Commercial speech received no protection until 1976. In *Valentine v. Chrestensen*, the Court held that commercial speech involving promoting a product for sale is not protected by the First Amendment. 316 U.S. 52, 62 (1942). The Court overruled *Valentine* in *Virginia Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (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.* The Court developed protection of commercial speech in several cases. See, e.g., *Greater New Orleans Broadcasting Ass’n, Inc. v. United States*, 527 U.S. 173 (1999); *Rubin v. Coors Brewing Co.*, 514 U.S. 476 (1995); *Bolger v. Youngs Drug Products Corp.*, 463 U.S. 60 (1983). For a history on the development of the commercial speech doctrine, see Alex Kozinski & Stuart Banner, *Who’s Afraid of Commercial Speech?* 76 VA. L. REV. 627 (1990).

³³² *Sorrell*, 131 S. Ct. at 2679 (Breyer, J., dissenting).

context. 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 *Sorrell*, the Court stated that the “First Amendment requires heightened scrutiny whenever the government creates ‘a regulation of speech because of disagreement with the message it conveys.’”³³³ In that case, the Court found that the purpose of the law was “viewpoint discriminatory.”³³⁴ 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 accuracy of information is ensured by requiring that drugs go through the pre-market approval process. Of course, the government seeks to enforce its pre-market 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. The court merely concluded that the goal and impact of the restriction was to decrease off-label drug marketing.³³⁵

In his dissent in *Sorrell*, 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.³³⁶ 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 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.”³³⁷

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 and effective.³³⁸ 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”³³⁹ In *Caronia*, the court erroneously concluded that the restriction did not directly advance the government’s interest because off-label use is

³³³ *Sorrell*, 131 S. Ct. at 2664.

³³⁴ *Id.* at 2663.

³³⁵ *Caronia*, 703 F. 3d at 165.

³³⁶ *Sorrell*, 131 S. Ct. at 2678 (Breyer, J., dissenting).

³³⁷ *Sorrell*, 131 S. Ct. at 2678 (Breyer, J., dissenting). In *Sorrell*, 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. It reawakens *Lochner*’s pre-New Deal threat of substituting judicial for democratic decisionmaking where ordinary economic regulation is at issue.” *Id.* at 2685.

³³⁸ *See, e.g., Caronia*, 703 F. 3d 149, 166 (citing *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.”)).

³³⁹ 13 F. Supp. 2d 51, 72 (D. D.C. 1998).

lawful.³⁴⁰ In doing so, the court did not give adequate consideration to the distinction between off-label prescribing and off-label promotion.³⁴¹ Off-label prescribing allows doctors to make scientifically sound medical decisions about individual patients,³⁴² 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.³⁴³ The FDA recognizes that off-label uses may be valuable,³⁴⁴ and seeks to avoid intrusion on the discretionary decisions of healthcare professionals.³⁴⁵ 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 interest 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 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.³⁴⁶ The Court then proceeded to list several other methods the government might employ to better regulate off-label promotion.³⁴⁷

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 post-market 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

³⁴⁰ *Caronia*, 703 F. 3d at 166.

³⁴¹ 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 ARCH. OF INTERNAL MED. 1280 (2005) (more than one fourth of nursing home residents received antipsychotic medications; many prescriptions were off-label and/or exceeded dosage guidelines).

³⁴² See GROOPMAN, *supra* note 317, at 218.

³⁴³ 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).

³⁴⁴ See *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 350 (2001).

³⁴⁵ See *id.*

³⁴⁶ *Caronia*, 703 F.3d at 167-68.

³⁴⁷ *Id.* at 168. See *supra* note 178.

denied effective treatment while others risk serious side effects without any benefit that would justify the risk.³⁴⁸

CONCLUSION

While 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 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 it outside of the scope of First Amendment protection. Furthermore, sound arguments distinguish the oral promotional statements by pharmaceutical representatives from the speech the Supreme Court found constitutionally protected in *Western States* and *Sorrell*. Prohibitions on off-label promotion are not subject to the heightened scrutiny standard the Court employed in *Sorrell* 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. 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.

³⁴⁸ Waxman, *supra* note 1, at 300.

