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Abstract

The FDA prohibits drug manufacturers from promoting approved drugs off-label despite the fact that physicians are free to prescribe FDA-approved products for any purpose they believe is indicated. In recent years the FDA’s prohibition on “off-label” drug promotion has been challenged, unsuccessfully, as an undue burden on commercial speech. However, in 2011 the U.S. Supreme Court in Sorrell v. IMS Health Inc. held that a regulation presenting both content- and speaker-based burdens on protected speech would be reviewed under a “heightened” level of First Amendment scrutiny, rather than the intermediate level of scrutiny previously applied to matters involving commercial speech. In the criminal case of United States v. Caronia, the Second Circuit Court of Appeals imposed this heightened level of scrutiny in a matter challenging the FDA’s prohibition of off-label promotion and held in 2012 that the government cannot prosecute pharmaceutical representatives for engaging in speech that promotes lawful, albeit off-label, indications for FDA-approved products. Just three months later, in United States v. Harkonen, the Ninth Circuit Court of Appeals upheld the conviction of a physician/CEO who was accused of crafting a deceptive press release to boost sales of his company’s product off-label, despite his argument that the First Amendment protected the practice. This split in the circuits is expected to result in an eventual grant of certiorari by the U.S. Supreme Court.

I. Introduction

In December 2012, a divided three-judge panel of the United States Court of
Appeals for the Second Circuit, in United States v. Caronia,1 overturned the conviction of a pharmaceutical representative who was found to have engaged in face-to-face "off-label" marketing of the narcolepsy drug, Xyrem.2 Xyrem is a central nervous system depressant approved by the Food and Drug Administration (FDA) to treat narcolepsy and cataplexy in adults.3 A Schedule III controlled substance and known street drug of abuse, Xyrem is sometimes prescribed "off-label" to treat such conditions as fibromyalgia, schizophrenia, chronic fatigue syndrome, and severe "cluster" headaches in adults.4 FDA regulations prohibit pharmaceutical manufacturers from promoting drugs off-label despite the fact that physicians remain free to prescribe FDA-approved products for any purpose they believe is indicated.5 In recent years, however, pharmaceutical manufacturers have challenged the FDA's prohibition of off-label drug promotion as an undue burden on commercial speech.6

The majority in Caronia, the first appellate court to directly confront the issue, held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the Food, Drug and Cosmestic Act [FDCA] . . . for speech promoting the lawful, off-label use of an FDA-approved drug."7 In doing so, the court

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1 703 F.3d 149 (2nd Cir. 2012).
2 Id. at 169. Off-label drug use refers to the prescribing of a drug for an unapproved indication or an approved indication in an unapproved age group, dosage, or route of administration. Randall S. Stafford, Regulating Off-Label Drug Use — Rethinking the Role of the FDA, 358 NEW ENG. J. MED. 1427, 1427 (2008).
3 MAYO CLINIC, http://www.mayoclinic.com/health/drug-information/DR601707 (last visited Dec. 24, 2013). Xyrem (sodium oxybate) "is used to treat excessive daytime sleepiness and to reduce the number of cataplexy (weak or paralyzed muscles) attacks in people with narcolepsy. This medicine is a narcotic agent that is used for sedation." Id.
4 MAYO CLINIC, http://www.mayoclinic.com/health/cluster-headache/DS00487 (last visited Nov. 11, 2013). Cluster headaches, which occur in cyclical patterns, are an extremely painful form of headache that often awaken patients at night with intense pain in or around the eyes or one side of the head. Id. Off-label prescriptions include use in children. Hema Murali & Suresh Kotagal, Off-Label Treatment of Severe Childhood Narcolepsy-Cataplexy with Sodium Oxybate, 29 SLEEP 1025 (2006).
6 See Marcia M. Boumil, Off-Label Marketing and the First Amendment, 368 NEW ENG. J. MED. 103, 103 (2013).
7 Caronia, 703 F.3d at 169.
invalidated long-standing regulations intended to prevent drug companies from promoting drugs for off-label use.\(^8\)

Three months later in *United States v. Harkonen*, the Ninth Circuit upheld the wire fraud conviction of W. Scott Harkonen, Chief Executive Officer of the pharmaceutical company InterMune.\(^9\) At the trial level, the jury found that Harkonen crafted a press release that falsely represented the findings of a medical study on the drug Actimmune.\(^10\) The press release suggested that, based on the study, a particular off-label use of the drug could be beneficial to some patients.\(^11\)

The decisions in *Caronia* and *Harkonen* both came in the wake of the United States Supreme Court decision in *Sorrell v. IMS Health Inc.*\(^12\) *Sorrell* involved a commercial data vendor that challenged a Vermont law permitting data mining of prescriber-identifiable records for some purposes but not others.\(^13\) The Supreme Court held that a law that constrains commercial speech on the basis of its content and its speaker would be reviewed for First Amendment purposes using a standard of "heightened" constitutional scrutiny.\(^14\) While acknowledging the importance of Vermont's asserted interests in medical privacy and reduction of health care costs, the Court nevertheless concluded that Vermont's data mining prohibition unduly restricted free speech and therefore was unconstitutional.\(^15\)

*Caronia*, *Sorrell*, and other recent Supreme Court cases addressing the scope of the First Amendment raise important questions about whether state and federal governments can enforce a host of regulatory programs that target particular conduct or

\(^10\) *Id.* at 635. "Actimmune is a synthetic version of interferon gamma-1b, a naturally occurring biologic response modifier. FDA has approved Actimmune to decrease the number and severity of infections in patients with chronic granulomatous disease and to delay the progression of severe, malignant osteoporosis." FOOD AND DRUG ADMIN., http://www.fda.gov/Drugs/ DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm109130.htm (last visited Dec. 24, 2013).
\(^11\) *Harkonen*, 510 F.Appx. at 636.
\(^12\) *Caronia*, 703 F.3d at 164; *Harkonen*, 510 F.Appx. at 633; *Sorrell* v. IMS Health Inc., 131 S. Ct. 2653 (U.S. 2011).
\(^13\) *Sorrell*, 131 S. Ct. at 2656. The law permitted data mining for some purposes, such as research, but not for others, primarily marketing, in order to advance the state's interest in limiting the promotion of expensive, brand-name drugs. *Id.* at 2656-57.
\(^14\) *Id.* at 2663-64.
\(^15\) *Id.* at 2659.
industries. Justice Breyer, writing for the dissent in Sorrell, forewarned that permitting such a wide construction of the First Amendment could put at risk important regulations, such as the FDA prohibition of off-label drug promotion necessary to combat false and misleading speech.

Section I of this article reviews the current FDA guidelines concerning off-label promotion of FDA-approved drugs. It discusses the FDA’s distinction between activities the agency believes constitute “scientific exchange” (which are permitted) versus those it believes primarily amount to the “marketing” of products (which are not). Section II reviews representative cases in which the Department of Justice (DOJ) claimed a violation of the FDCA misbranding provisions in the context of scientific exchange. Section III reviews the U.S. Supreme Court’s opinion in Sorrell, particularly with respect to its application of heightened scrutiny to commercial speech under the First Amendment. Section IV discusses the opinions of the District Court and Second Circuit in Caronia, informed by doctrine established in Sorrell. Section V reviews the Ninth Circuit’s opinion in Harkonen, which created a split in the circuits and the opportunity for eventual Supreme Court review. Section VI concludes with the implications of Caronia and Harkonen on FDA authority and policy.

I. Background: Off-Label Promotion of Drugs and Devices under Existing FDA Guidelines

The FDA, pursuant to the FDCA, is vested with the authority to oversee the safety of pharmaceutical production, sales, and marketing. A drug label contains the established name of the drug, its ingredients, indications, and directions for use, as well as a brief statement of its side effects, contraindications, and effectiveness. Failure to provide this information in the label or to “prescribe, recommend, or suggest” that the

16 See id. at 2658; Caronia, 703 F.3d at 168-69.
17 Sorrell, 131 S. Ct. at 2675-76 (Breyer, J., dissenting).
18 See infra Part I.
19 See infra Part I.
20 See infra Part II.
21 See infra Part III.
22 See infra Part IV.
24 See infra Part VI.
drug is appropriate for a non-FDA-approved indication is considered "misbranding" by the FDA, and may result in civil and criminal penalties. The FDA prohibits a manufacturer from promoting a drug for an unapproved indication. Therefore, once a drug is FDA-approved for at least one indication and placed into interstate commerce, medical providers are free to prescribe it for any purpose, regardless of its labeling, subject only to professional standards. As previously stated, when a drug is used for a condition or in a manner that deviates from that described in the FDA-approved drug label, the use is considered off-label. This includes the use of the drug to treat a different medical condition or disease, as well as use in a dosage or route that deviates from that described in the approved label.

In 2011, the U.S. Supreme Court's opinion in Sorrell paved the way for

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33 See Randall S. Stafford, Regulating Off-Label Drug Use — Rethinking the Role of the FDA, 358 NEW ENG. J. MED. 1427, 1427 (2008). See also Kessler, supra note 32, at 288 (discussing federal government's need to balance safety of patients while accelerating availability of new drugs).
reconsideration of the FDA’s prohibition of off-label promotion of approved drugs.\textsuperscript{34} In \textit{Sorrell}, the Supreme Court reviewed the constitutionality of a Vermont statute that restricted the ability of pharmaceutical companies to purchase certain prescriber-identifiable data ("PI data") for subsequent use in the marketing of their products.\textsuperscript{35} Specifically, the Court considered whether a Vermont law prohibiting the sale and use of prescriber-identifiable pharmacy records under certain circumstances unduly burdened commercial speech.\textsuperscript{36} In striking down the law, the Court held that because the statute imposed both content- and speaker-based burdens on protected speech, it would be reviewed under a "heightened" level of First Amendment scrutiny.\textsuperscript{37} Application of this more stringent standard, rather than the intermediate level of scrutiny previously applied to commercial speech, proved fatal to the Vermont law.\textsuperscript{38}

Both the majority and dissenting opinions in \textit{Sorrell} acknowledged the potential consequences of imposing heightened scrutiny on the FDA’s regulation of commercial speech.\textsuperscript{39} The majority did not explicitly speak to regulations concerning off-label promotion, instead disposing of the issue by commenting that nothing in the opinion affects regulations designed to combat false and misleading speech.\textsuperscript{40} The dissent explicitly identified the potential impact of \textit{Sorrell} as it might apply to off-label marketing of approved drugs.\textsuperscript{41} At the time \textit{Sorrell} was decided, \textit{Caronia} was pending in the Second Circuit and poised to be the first appellate decision to address this potential implication of the Supreme Court’s heightened level of First Amendment scrutiny. In view of the importance of this issue, the Second Circuit ordered the parties to provide supplemental briefs addressing the impact of \textit{Sorrell} on its pending decision in \textit{Caronia}.\textsuperscript{42}

Challenging his conviction for off-label promotion, commonly known as "misbranding" of an FDA-approved drug, Caronia contended that the FDA may not prohibit truthful and non-misleading commercial speech in the marketing of a

\textsuperscript{34} See \textit{Sorrell} v. IMS Health Inc., 131 S. Ct. 2653, 2672; 2675–76 (Breyer, J., dissenting) (2011).
\textsuperscript{35} Id. at 2659-60.
\textsuperscript{36} Id. at 2656.
\textsuperscript{37} Id. at 2657-58.
\textsuperscript{38} Id. at 2658.
\textsuperscript{40} \textit{Sorrell}, 131 S. Ct. at 2672.
\textsuperscript{41} Id. at 2675–76 (Breyer, J., dissenting).
pharmaceutical product, whether on or off-label. The federal district court for the Eastern District of New York disagreed, holding that "constraining the marketing options of manufacturers is one of the 'few mechanisms available' to the FDA 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." The district court found the FDA regulations to be a valid exercise of governmental authority. It concluded that "any right Caronia had as Xyrem's sales representative to express as commercial speech the truthful promotion of Xyrem's off-label uses is not unconstitutionally restricted by the misbranding provisions" of the FDCA.

Historically, the FDA has claimed that prohibiting pharmaceutical manufacturers from promoting off-label use of their products achieves three important government interests: promoting the health and safety of the public, ensuring that physicians receive accurate and unbiased information regarding prescription choices, and preserving the effectiveness and integrity of the FDA's drug approval process. The agency's concerns are grounded in practicality because prescribers, as well as patients, look to the drug label as a reliable source of information about the drug. Misinformation concerning approved uses and outcomes can result in medication errors, untoward drug reactions, and unanticipated side effects. Indeed, media reports of side effects and increased risks associated with off-label use of FDA-approved drugs are rampant.

44 Id. at 401 (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998)). The court heeded a 2008 cautionary note from the Seventh Circuit 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" and concluded that it could not identify a less restrictive manner in which to prohibit pharmaceutical companies from circumventing the FDA approval process. Id. at 400-01 (quoting United States v. Caputo, 517 F.3d 935, 940 (7th Cir. 2008)).
45 Caronia, 576 F. Supp. 2d at 401.
46 Id. at 402.
49 Caronia, 576 F.Supp.2d at 392-93.
50 See generally Ava Lawson, Off Label Risperdal Use in Nursing Homes Still Rampant, Injury Lawyer News (September 13, 2013), http://injurylawyer-news.com/2013/09/off-label-risperdal-use-nursing-homes-still-rampant/; see also Evelyn Pringle, Consequences of Rampant Off-Label Prescribing of
recombinant coagulation Factor VIIa hemostatic agent approved by the FDA in 1999 to treat patients with a particular blood-clotting protein deficiency and certain hemophiliacs.\textsuperscript{51} Due to the drug's ability to immediately control bleeding, physicians began using NovoSeven for such off-label purposes as uncontrollable bleeding during general surgeries, heart surgery, and hemorrhagic stroke.\textsuperscript{52} In fact, a 2011 study analyzing prescribing habits in 615 non-federal U.S. hospitals from January 2000 to December 2008 concluded that 97 percent of the more than 18,000 in-hospital uses of Factor VIIa were for off-label indications.\textsuperscript{53} However, a subsequent 2011 study of this off-label indication determined that use of Factor VIIa off-label for heart surgery or hemorrhagic stroke patients not only failed to improve survival, but actually increased the likelihood of thromboembolism, or a blood clot, in the heart or brain.\textsuperscript{54} The study reported that one out of every 20 heart surgery patients who received Factor VIIa could be expected to suffer a serious thromboembolism in the heart or brain, and one out of every 17 hemorrhagic stroke patients could be expected to have a serious thromboembolism.\textsuperscript{55}

It has long been recognized that "because the pace of medical discovery runs ahead of the FDA's regulatory machinery, the off-label use of some drugs is frequently considered to be 'state-of-the-art' treatment."\textsuperscript{56} Indeed, many off-label uses of FDA-approved drugs are beneficial, and further study has led to additional approved uses.\textsuperscript{57} For instance Rituxan, a drug initially approved for the treatment of specific types of non-Hodgkin's lymphoma, proved so effective that physicians were regularly prescribing the drug off-label for other cancers and immune system disorders.\textsuperscript{58} The prominent

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\textsuperscript{52} Id.
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\textsuperscript{53} Aaron C. Logan, Veronica Yank & Randall S. Stafford, Off-Label Use of Recombinant Factor VIIa in U.S. Hospitals: Analysis of Hospital Records, 154 ANNALS INTERNAL MED. 516, 520 (2011).\textsuperscript{54}
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Veronica Yank et al., Systematic Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications, 154 ANNALS INTERNAL MED. 529, 536 (2011).\textsuperscript{55}
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Kolata, supra note 51, at D1. In response to these off-label findings, Dr. Jerry Avorn, Professor of Medicine at Brigham and Women's Hospital in Boston, Massachusetts, remarked: "It's scary... [t]his is a powerful drug, and we don't fully understand it." Id.\textsuperscript{56}
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See Stafford, supra note 33, at 1427-29.
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unapproved use of Rituxan eventually resulted in the manufacturer conducting clinical trials for these subsequent indications, and Rituxan is now also indicated on-label for chronic lymphocytic leukemia and rheumatoid arthritis.\textsuperscript{59}

In light of the regulatory ban on off-label promotion of FDA-approved drugs, the primary source of beneficial off-label drug information is physicians themselves, communicated through scientific papers, meetings, and lectures such as Grand Rounds.\textsuperscript{60} These forms of "scientific exchange" are specifically and intentionally unrelated to the promotion or marketing of the drug.\textsuperscript{61} Those contributing to the medical and scientific literature freely discuss the suitability of approved drugs for off-label uses.\textsuperscript{62} Medical literature is replete with discussions of clinical trials studying off-label uses of FDA-approved drugs, some of which are eventually submitted for FDA approval.\textsuperscript{63} In addition, the various medical specialties offer treatment or practice "guidelines" based upon information contained in the medical literature.\textsuperscript{64} These guidelines, often derived from clinical trials, may also include off-label uses of approved medication. Some even constitute the standard of care for certain medical conditions.\textsuperscript{65}

\textsuperscript{59} Id.
\textsuperscript{60} See, e.g., Public Health Grand Rounds, CENTERS FOR DISEASE CONTROL & PREVENTION, available at http://www.cdc.gov/about/grand-rounds/ (last visited Dec. 24, 2013). Grand Rounds refers to a series of presentations delivered on a regular basis to promote medical education and clinical care, often highlighting advances in the field. \textit{Id.}


\textsuperscript{62} See Richardson v. Miller, 44 S.W.3d 1, 13 (Tenn. Ct. App. 2000). In Richardson, the court emphasized that, “[P]hysicians may use approved drugs or devices in any way that they, in their professional judgment, believe will best serve their patients, regardless of whether the FDA has approved the drug or device for that particular use." \textit{Id.}

\textsuperscript{63} Mullins, CD et al., Recommendations for Clinical Trials of off Label Drugs Used to Treat Advanced Stage Cancer, 30 J. CLIN. ONCOL. 661, 661-6 (2012).


Physicians, scientists, and medical researchers may also use an approved drug for "investigational use" in the context of a clinical study protocol investigating alternate uses of a drug. When one of the purposes of the "investigational use" is for supporting a significant change in the promotion or advertisement of the drug, however, the proponents of the new use must submit an "Investigational New Drug" application and must also submit to review by an institutional review board (IRB). Otherwise, regardless of the extent or prestige or common knowledge of scientific evidence indicating that the product is safe and effective for an off-label use, the drug cannot be promoted for such use. The prohibition on off-label promotion thus serves as a powerful incentive for drug manufacturers to: continue to conduct organized studies on their products; investigate alternative uses; report to the FDA untoward side effects; and generally contribute to the literature about the safety, effectiveness, dosage requirements, and limitations of their drugs. A manufacturer's failure to comply with the rigorous FDA rules before promoting an off-label use is not only illegal; it may also result in liability for prescribers if the off-label use results in a poor medical outcome.

Drug manufacturers routinely take advantage of what was, prior to 2006, a scientific-exchange "safe harbor." This "safe harbor" allowed drug manufacturers to distribute to physicians scientific literature, such as peer-reviewed journal articles, that discussed off-label indications for FDA-approved products. While the safe harbor no longer applies, "FDA Guidance," revised most recently in 2009, concerning "good

69 See Richardson v. Miller, 44 S.W.3d 1, 12 (Tenn. Ct. App. 2000).
72 See id. If certain conditions specified in FDAMA Section 401 were met, such distribution could not be introduced as evidence of the manufacturer's intent to promote the product for an unapproved use. Id.
reprint practices” for dissemination of scientific literature discussing off-label uses of approved drugs is available. In general, the FDA Guidance provides that distribution is permissible if the publication’s editorial board: (1) includes experts in the subject matter of the article, free of bias or conflicts of interest; (2) the article is peer-reviewed in accordance with the organization’s usual peer-review processes; (3) the publication is not funded by the manufacturer of the drug that is the subject of the journal article; and (4) the article is not false or misleading. Finally, the literature as distributed may not be abridged, summarized, or highlighted. Notably, while the FDA provides this Guidance to manufacturers, it does not pre-approve materials for distribution and reserves the right to determine after-the-fact whether a manufacturer has violated its rules. Nor does the Guidance document create or prohibit any conduct or establish rights for parties; rather, it solely acts as an updated safe harbor.

Not surprisingly, there has been vigorous criticism of the FDA Guidance document. For instance, the New York State Department of Health, via comments to the FDA regarding the draft Guidance document, argued that in light of the broad power provided to the FDA to regulate off-label promotion and the documented history of inappropriate off-label marketing by pharmaceutical companies, the Guidance document unacceptably increases tolerance for pharmaceutical conduct that may constitute illegal off-label promotion.

73 Id. at 1; 21 C.F.R. § 202.1 (2013) (describing prescription drug advertisements).
74 U.S. 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 4 (2009), available at http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf. Further, the journal must require a well-controlled clinical investigation that is scientifically valid, balanced, and fully addresses safety and efficacy of the off-label use that is the subject of the article. Id.
75 Id. at 5.
76 Id. at 6.
77 N.Y. STATE DEP’T OF HEALTH, COMMENTS OF THE NEW YORK STATE DEPARTMENT OF HEALTH CONCERNING THE UNITED STATES FOOD AND DRUG ADMINISTRATION’S DRAFT 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 1-2 (2008), available at http://www.health.state.ny.us/professionals/patients/medicines/prescription/docs/comments_submitted_to_the_fda.pdf. As the New York State Department of Health points out, this means that any conduct that falls outside of the guidance document may or may not be a violation of the FDCA. Id.
78 See infra notes 79-80 and accompanying text.
The pharmaceutical industry also found fault with the document, criticizing its ambiguity.\textsuperscript{80} Immediately following the release of the U.S. Supreme Court decision in \textit{Sorrell}, the FDA received a citizen petition on behalf of Allergan, Eli Lilly, Johnson & Johnson, Novartis, Pfizer, Novo Nordisk, and Sanofi-Aventis.\textsuperscript{81} The petition sought to require the Commissioner to clarify the FDA’s position on communication of off-label information, particularly in light of \textit{Sorrell}.\textsuperscript{82} At this time, the FDA has not yet responded to the petition.\textsuperscript{83}
II. Overview of Misbranding vs. Scientific Exchange: Setting the Legal Landscape

Thousands of regulatory actions and lawsuits, in both federal and state courts, have been launched against the pharmaceutical industry for off-label promotion of drug products. The FDA’s Division of Drug Marketing, Advertising, and Communications (DDMAC) bears responsibility for overseeing the promotional materials and activities of pharmaceutical companies and for identifying violations, including off-label promotion as a form of "misbranding." The DOJ’s pursuit of impermissible off-label promotional activities identified by DDMAC has been relentless. For example, between 2003 and 2007, DOJ enforcement actions against pharmaceutical companies led to eleven major settlements.

In June 2012, GlaxoSmithKline LLC (GSK) agreed to plead guilty to three misdemeanor FDCA violations and pay $3 billion in order to resolve criminal and civil liability arising from the company’s off-label promotion of two antidepressants, Paxil and Wellbutrin, as well as GSK’s failure to report mandatory safety data to the FDA regarding its diabetes drug, Avandia. The government alleged that GSK engaged in a

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86 See id.

87 Id at 28. These DOJ enforcement actions included the payment of $430 million in fines by Pfizer for off-label promotion of Neurontin, $515 million in fines by Bristol-Meyers Squibb for off-label promotion of Abilify, $635.5 million in fines by Purdue Frederick for off-label promotion of OxyContin, and $704 million in fines by Serono, S.A. for off-label promotion of Serostim. Id.

variety of egregious marketing practices, including wooing doctors with extravagant vacations, meals, concert tickets, and other perks in addition to assisting in the publication of a medical journal article that falsely reported clinical trial data suggesting Paxil had been proven effective for treating depression in children.\textsuperscript{89} The GSK resolution constituted the largest health care fraud settlement in U.S. history, and the total penalties—including a $956,814,000 criminal fine, $43,185,600 in forfeitures, and a $2 billion civil settlement amount—represented the largest payout ever by a pharmaceutical company.\textsuperscript{90}

Further, in August 2012, the largest-ever multistate consumer protection-based pharmaceutical fraud settlement occurred between Janssen Pharmaceuticals, Inc., the pharmaceutical division of Johnson & Johnson, the District of Columbia, and 36 states.\textsuperscript{91} The settlement concerned the promotion of Janssen's antipsychotic drugs, Risperdal and Invega.\textsuperscript{92} The settlement substantially limited the company's right to distribute certain peer-reviewed journal articles for promotional purposes that discuss


\textsuperscript{90} GSK Press Release, supra note 88. GSK also entered into a comprehensive, five-year Corporate Integrity Agreement with the Department of Health and Human Services' Office of Inspector General (OIG), which required the company to undertake major business reforms designed to avert the payment of kickbacks and other unlawful behavior in the future. See CORPORATE INTEGRITY AGREEMENT BETWEEN THE OFFICE OF INSPECTOR GENERAL OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND GLAXO SMITHKLINE LLC (2012), available at http://www.justice.gov/opa/documents/gsk/plea-ex-d.pdf. For example, GSK was forced to stop basing compensation for its drug representatives on territorial sales goals, in addition to implementing "clawback" mechanisms that would allow the company to recoup bonuses and other long-term incentives from executives responsible for significant misconduct. Id. at 32–33, App. E; see also David Ingram, GlaxoSmithKline Settles Healthcare Fraud Case for $3 Billion, REUTERS (July 2, 2012, 3:02 PM), http://www.reuters.com/article/2012/07/02/us-glaxo-settlement-idUSBRE8610S720120702.


off-label uses. Specifically, the settlement specified that articles could be used for marketing purposes only after Janssen filed a supplementary application with the FDA for the approval of the drug for the then off-label use.

Notwithstanding these settlements, drug manufacturers have continued to challenge the FDA regulations on misbranding, in particular citing First Amendment protection of commercial speech. For example, in October 2009, the pharmaceutical manufacturer Allergan, Inc. sought declaratory relief based upon the FDA’s prohibitions against off-label promotion of Botox, an Allergan product. Botox is approved for treating certain muscle dystonias, or spasms, but reportedly has been recognized in the literature as the standard of care, off-label, for spasticity. Following a February 8, 2008 communication from the FDA regarding adverse reactions to Botox injections, particularly in children, the FDA required that Allergan issue updated warnings regarding the potential for Botox to spread beyond the local injection site. Allergan filed a complaint alleging that it sought to communicate specific and more detailed risks associated with the use of Botox than the FDA suggested, but that “misbranding” principles precluded the company from doing so.

93 Judy Greenwald, Johnson & Johnson to Pay $181M to Settle Charges of Off-Label Drug Marketing, BUSINESS INSURANCE (Aug. 30, 2012), http://www.businessinsurance.com/article/20120830/NEWS07/120839984#. “The settlement prohibits Janssen from making false, misleading or deceptive claims regarding Risperdal or Invega, and requires it to report clinical research results regarding the drugs in an “accurate, objective and balanced manner . . . .” Id.


99 Complaint at 24-25, Allergan, Inc. v. United States, No. 09-cv-1879 (D.D.C. Oct. 1, 2009). [T]he Allergan were to engage in the speech it proposes, as outlined above, much of its speech
In response, the FDA sought dismissal on grounds that Allergan’s action was not ripe since the FDA had not yet applied the challenged statute and regulations.\(^\text{100}\) A few months later, Allergan pled guilty to criminal misbranding (off-label promotion) of Botox in a negotiated settlement with the DOJ.\(^\text{101}\) Additionally, Allergan paid $375 million for the criminal violations and $225 million to resolve outstanding civil claims brought by the DOJ under the civil False Claims Act.\(^\text{102}\)

One of the more notorious “misbranding” matters, which set the stage for the current debate regarding activities that constitute “scientific exchange” versus those that amount to marketing, was demonstrated in *United States ex rel. Franklin v. Parke-Davis*, in regards to Parke-Davis’s off-label promotion of its blockbuster drug, Neurontin.\(^\text{103}\) The case originally began in 1996 when David Franklin, a research fellow at Harvard Medical School, was engaged by Parke-Davis as a “medical liaison” speaking and consulting for the company.\(^\text{104}\) Shortly after resigning from Parke-Davis after only five months, Franklin filed a *qui tam* (whistleblower) lawsuit.\(^\text{105}\) In the suit, Franklin alleged that he would fall within the FDA’s expansive definition of ‘labeling’ [found in] 21 C.F.R. § 202.1(1)(2). The FDA thus would deem Botox® ‘misbranded’ if, in such expression, Allergan made any scientific claims that the FDA had not previously approved, on the theory that unapproved speech is inherently ‘false or misleading.’...Allergan fears that its expression of true medical information would be deemed by the Government to be a ‘suggestion’ that Botox® be used to treat spasticity, and thus expression of such information also would give rise to a substantial risk that Allergan would be prosecuted for distributing an unapproved ‘new drug.’


\(^{100}\) Defendants’ Memorandum of Points and Authorities in Support of Motion to Dismiss or for Summary Judgment at 2, Allergan, Inc. v. United States, No. 09-cv-1879 (D.D.C. Dec. 11, 2009).


\(^{104}\) *Parke-Davis*, 147 F. Supp. 2d at 44.

\(^{105}\) *Id.* at 45. The Civil False Claims Act, 31 U.S.C. § 3729(a)(1) (2010), which prohibits the
and other medical liaisons were instructed by Parke-Davis to make exaggerated or false claims concerning the safety and efficacy of Neurontin for off-label uses. Specifically, Franklin alleged that he was trained to suggest that Neurontin was approved in specific doses by the FDA for use as an adjunctive treatment for epilepsy and was safe and effective for a variety of off-label uses and in dosages greater than that originally approved by the FDA. He further alleged that the medical liaisons were “encouraged to misrepresent their scientific credentials and to pose as research personnel, rather than as sales representatives” in order to bolster their presentation to physicians.

Franklin further exposed what he believed was a serious flaw in the “scientific exchange” theory of dissemination of studies. Specifically, he alleged that Parke-Davis’s “medical liaisons” were expected to present to physician audiences as though they were impartially discussing scientific literature, when in fact they were introducing sham studies that “had no scientific value.” Additionally, according to Franklin, Parke-Davis hid its activities from the FDA by routinely shredding or falsifying documents, encouraging “medical liaisons” to conceal the off-label nature of the recommended uses and suggesting that physicians avoid leaving a paper trail. Franklin estimated that fifty percent of Neurontin’s sales in 1996 were a result of off-label use. In May 2004, the penalty proved to be equally steep. Pfizer, the successor to Parke-Davis, entered into a settlement agreement, paying $430 million in fines after pleading guilty to FDCA statutory violations.

In more recent qui tam litigation, Dr. Jeremy Garrity, an Associate "submission of a false . . . claim to the government for payment," enjoys frequent use primarily due to its qui tam, or whistleblower provisions. Christopher D. Zalesky, Pharmaceutical Marketing Practices: Balancing Public Health and Law Enforcement Interests; Moving Beyond Regulation-Through-Litigation, 39 J. HEALTH L. 235, 245 (2006). This provision allows private entities, like David Franklin, to bring claims on behalf of the government, and if successful, collect a portion of the government’s monetary settlement in the case. See id.

106 Parke-Davis, 147 F. Supp. 2d at 45.
107 Id.
108 Id.
109 See Citizen Petition, supra note 82.
110 Parke-Davis, 147 F. Supp. 2d at 46.
111 Id.
112 Id. at 45.
113 See Warner-Lambert to Pay $430 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion, DEPARTMENT OF JUSTICE, available at http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm. In addition, Franklin was rewarded as a whistleblower to the tune of approximately $25 million. Id. Pfizer also agreed to enter into a Corporate Integrity Agreement. Id.
Cardiovascular Metabolic Specialist and Area Scientific Sales Consultant for Novartis Pharmaceutical Corporation, brought a relator's suit against Novartis. Garrity alleged, inter alia, that the FDA had issued a warning letter to Novartis to "immediately cease the dissemination of all promotional materials for [its drug,] Diovan[,] that contained claims [not approved in its label]." Garrity further claimed that Novartis continued to market Diovan off-label despite the FDA's warning, even using the same slide presentation. He further alleged that the sales force was specifically directed to, and did, market another Novartis product off-label. According to Garrity, "[u]niform and widespread tactics used by [Novartis] to promote off-label, in conjunction with kickbacks, also included hiding behind 'CME' Speaker Programs via physicians and other healthcare providers to promote off-label usage." Presumably without admitting liability, Novartis settled the suit just one month after it was filed, agreeing to pay $422.5 million in civil and criminal fines.

III. Commercial Speech Redefined: Sorrell v. IMS Health Inc. and its Impact on Off-Label Promotion

The argument that off-label promotion constitutes "speech," and thus should enjoy some level of protection under the First Amendment, was recently forecast in the U.S. Supreme Court decision in Sorrell v. IMS Health Inc. There, the U.S. Supreme Court considered whether a Vermont law attempting to prevent pharmaceutical companies from purchasing or using PI data survived constitutional scrutiny under the First Amendment. At issue in Sorrell was a process known as data mining, through which data companies purchase prescription-related information (i.e., the prescriber's
name and address; the drug's name, dosage, and quantity; the patient's age and gender; and the date and location the prescription is filled) from pharmacies and others, thereby allowing them to construct comprehensive profiles of physicians' prescribing habits. These bundles of information are then sold to pharmaceutical companies, whose marketing divisions in turn use the PI data to craft and tailor their sales pitches prior to representatives making a sales call, or "detail." Specifically, the issue before the Sorrell Court was whether Vermont's Prescription Confidentiality Law, restricting this use of PI data, unduly burdened pharmaceutical companies and data miners' First Amendment commercial speech rights.

In striking down the law, the Supreme Court held the Vermont statute imposed both content- and speaker-based burdens on protected speech, thus justifying the application of "heightened" First Amendment scrutiny to analyze the speech restrictions. In prior cases, the Court had resorted to an intermediate level of scrutiny as the standard to be applied in matters implicating commercial speech. Under a four-part test established in the landmark Central Hudson Gas & Electric Corp. v. Public Service


123 Sorrell, 131 S. Ct. at 2659-60.

124 See VT. STAT. ANN. tit. 18, § 4631(d) (2013). In pertinent part, the statute provided that:

A health insurer, a self-insured employer, an electronic transmission intermediary, a pharmacy, or other similar entity shall not sell, license, or exchange for value regulated records containing prescriber-identifiable information, nor permit the use of regulated records containing prescriber-identifiable information for marketing or promoting a prescription drug, unless the prescriber consents . . . . Pharmaceutical manufacturers and pharmaceutical marketers shall not use prescriber-identifiable information for marketing or promoting a prescription drug unless the prescriber consents . . . .

Id. See also Sorrell, 131 S. Ct. at 2660. The Court granted certiorari to resolve a split between the First Circuit, which had upheld the constitutionality of similar laws enacted by New Hampshire and Maine, and the Second Circuit, which had invalidated the Prescription Confidentiality Law. See generally IMS Health Inc. v. Sorrell, 630 F.3d 263 (2d Cir. 2010); IMS Health Inc. v. Mills, 616 F.3d 7 (1st Cir. 2010) (Me.); IMS Health Inc. v. Ayotte, 550 F.3d 42 (1st Cir. 2008) (N.H.).

Commission of New York case, commercial speech was deemed immune from First Amendment protection if: (1) the speech at issue is lawful and not misleading; (2) the government asserts a substantial state interest; (3) the regulation directly advances that purported interest; and (4) the regulation is no more extensive than necessary to achieve that interest. The Sorrell Court, however, departed from its traditional commercial speech analysis because it viewed Vermont's prohibition on the sale, disclosure, and use of PI data as a pernicious regulation that disfavored particular speakers, like data miners and pharmaceutical manufacturers, and particular content, namely marketing messages. The Sorrell majority called attention to what it viewed as blatant discrimination by Vermont against participants in the data mining industry. The majority also noted the apparent favoritism of academic organizations and governmental agencies – entities that remained at liberty to obtain and use PI data "in countering the messages of brand-name pharmaceutical manufacturers and in promoting the prescription of generic drugs." Such disadvantageous treatment was further evidenced in the Court's eyes by the legislature's findings expressing the intent to undermine the reach and effectiveness of brand-name pharmaceutical marketing. Additionally, the majority rejected Vermont's contention that the Prescription Confidentiality Law represented a mere regulation of commercial activity, further holding that the statute "impose[d] more than an incidental burden on protected expression" in light of the restriction's "content- and speaker-based" overtones. Acknowledging that "it is all but dispositive to conclude that a law is content-based and, in practice, viewpoint-discriminatory," the Sorrell Court went on to explain why, in any event, Vermont's law failed the Central Hudson test. With respect to the governmental interests at stake, Vermont contended that the Prescription Confidentiality Law was critical to protect medical privacy, including "physician confidentiality, avoidance of

128 Sorrell, 131 S. Ct. at 2663.
129 Id.
130 Id. The majority likened the restriction to a law barring trade magazines from purchasing or using ink, reasoning that depriving data miners and pharmaceutical companies of the "mere commodity" of PI data would impose a targeted burden on otherwise protected expression. Id. at 2667.
131 Id. at 2663-64. Specifically, the Court found objectionable language in the legislative findings asserting that detailers' messages "are often in conflict with the goals of the state" and that the 'marketplace for ideas on medicine safety and effectiveness is frequently one-sided in that brand-name companies invest in expensive pharmaceutical marketing campaigns to doctors." Id. at 2661 (quoting 2007 Vt. Acts & Resolves No. 80, §§ 1(3), (4)).
132 Sorrell, 131 S. Ct. at 2665.
133 Id. at 2667-68.
harassment, and the integrity of the doctor-patient relationship.”

Though the Court recognized the importance of medical privacy in the abstract, Vermont's law was not crafted to protect confidentiality in light of its myriad exceptions allowing nearly anyone other than pharmaceutical manufacturers and data miners to use PI data for virtually any purpose other than marketing. Even an “opt-in” provision, whereby Vermont doctors could consent to the otherwise impermissible sale and use of their PI data, did not save the statute from invalidity because the choice to opt in was, in the Court's view, contrived. Considering the statute's prohibitions applied only to pharmaceutical companies and data miners, a non-consenting physician would in reality obtain “a limited degree of privacy” in exchange for “acquiescing in the State's goal of burdening disfavored speech by disfavored speakers.”

Vermont also sought to justify the Prescription Confidentiality Law as a necessary tool to rein in spiraling healthcare costs and improve public health by ensuring that prescribing decisions were based upon unbiased, scientifically sound information. Again, the Court acknowledged the propriety of these goals, but held that Vermont's statute did not advance them in a constitutionally permissible manner. The Court emphasized that, “the First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.”

While Vermont remained free to express its own views about the merits of generic versus brand-name drugs through educational programming, counter-detailing efforts or otherwise, the state had improperly burdened speech that it found too persuasive “in order to tilt public debate in a preferred direction.” Perhaps, in an attempt to disclaim any effect its ruling might have on the FDA's campaign against off-

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134 Id. at 2668.
135 Id. Here, the court contrasted Vermont's law with the narrow disclosure exceptions under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), 42 U.S.C. § 1320d-2, and emphasized that, “[Vermont] did not enact a statute with [HIPAA’s] purpose or design. Instead, Vermont made prescriber-identifying information available to an almost limitless audience[,] . . . allow[ing] the information to be studied and used by all but a narrow class of disfavored speakers.” Id.
136 Id. at 2668-69.
137 Sorrell, 131 S. Ct. at 2669.
138 Id. at 2670.
139 Id. at 2661, 2670. Vermont unhelpfully appeared to back away from these policy objectives at oral argument, rejecting any suggestion that the Prescription Confidentiality Law's purpose and practical effect was to undermine detailers' influence on prescribers' behavior. Transcript of Oral Argument at 5–6, Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011) (No. 10-779).
140 Sorrell, 131 S. Ct. at 2671 (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996) (internal quotations omitted)).
141 Id.
label promotion, the *Sorrell* Court cursorily hinted that the agency "might defend" such regulations on grounds that the restrictions — unlike Vermont's Prescription Confidentiality Law — "will prevent false or misleading speech."\(^\text{142}\)

Justice Breyer, joined in the dissent by Justices Ginsburg and Kagan, gave more extensive treatment to the off-label promotion issue.\(^\text{143}\) As an initial matter, Justice Breyer wrote that depriving data miners and pharmaceutical companies of useful sales messages was an economic regulation.\(^\text{144}\) Additionally, Justice Breyer felt that any speech Vermont's statute infringed upon was commercial in nature and that the data mining regulation at issue satisfied the *Central Hudson* criteria.\(^\text{145}\) All three of Vermont's purported governmental interests were, in the dissent's view, "substantial" and "neutral" with respect to speech.\(^\text{146}\) The exhaustive legislative record demonstrated that Vermont had acted reasonably and in a way that would "directly advance" each of those objectives by providing doctors enhanced control over their confidential prescribing information.\(^\text{147}\) Moreover, Justice Breyer argued that the less-restrictive alternatives offered by the majority and the data mining industry would be ineffective in addressing the harms that Vermont had identified.\(^\text{148}\)

In conducting his analysis, Justice Breyer reiterated the clear distinction between a free marketplace for "social, political, esthetic, moral, and other ideas and experiences," and a free marketplace for goods and services.\(^\text{149}\) Given that "heightened scrutiny" is only appropriate with respect to the former category, Justice Breyer

\(^{142}\) *Id.* at 2672.

\(^{143}\) *Id.* at 2673-78 (Breyer, J., dissenting).


\(^{145}\) *Cent. Hudson*, 447 U.S. 557, 566 (1980); *Sorrell*, 131 S. Ct. at 2673 (Breyer, J., dissenting).

\(^{146}\) *Sorrell*, 131 S. Ct. at 2681 (Breyer, J., dissenting). The Court identified Vermont's interests as safeguarding medical privacy, reducing health care costs, and protecting public health. *Id.*

\(^{147}\) *Id.* at 2682-83 (Breyer, J., dissenting).

\(^{148}\) *Id.* at 2683-84. Justice Breyer also disputed the majority's assertion that Vermont's statute left PI data accessible to a limitless audience, insisting instead that "the disclosure-permitting exceptions [to the Prescription Confidentiality Law] are quite narrow, and they serve useful, indeed essential purposes" (e.g., encouraging physicians to close the door on detailers, establishing state-funded initiatives to educate doctors about the benefits of generics, etc.). *Id.* at 2684.

\(^{149}\) *Id.* at 2674 (Breyer, J., dissenting) (quoting *Fla. Bar v. Went For It, Inc.*, 515 U.S. 618, 623 (1995). In his dissent, Justice Breyer wrote "we have always been careful to distinguish commercial speech from speech at the First Amendment's core." *Id.*
maintained, “ordinary commercial or regulatory legislation that affects speech in less direct ways” is entitled to judicial deference.\textsuperscript{150} Raising the specter of a return to the dark days of the \textit{Lochner} era, Justice Breyer cautioned that, “apply[ing] a ‘heightened’ First Amendment standard of review whenever [a regulatory] program burdens speech would transfer from legislatures to judges the primary power to weigh ends and to choose means, threatening to distort or undermine legitimate legislative objectives.”\textsuperscript{151} Justice Breyer focused on the potential consequences \textit{Sorrell}'s brand of “heightened scrutiny” might have for regulatory actions taken by other states or federal agencies, including the FDA.\textsuperscript{152} According to Justice Breyer, the Prescription Confidentiality Law’s provisions formed part of a “traditional, comprehensive regulatory regime” governing the pharmaceutical industry.\textsuperscript{153} It is not uncommon – indeed, it is necessary, according to Justice Breyer – for regulatory programs to draw distinctions based on content or the identity of the speaker.\textsuperscript{154} To illustrate that point, Justice Breyer singled out the FDA’s ability to:

control in detail just what a pharmaceutical firm can, and cannot, tell potential purchasers about its products. Such a firm, for example, could not suggest to a potential purchaser (say, a doctor) that he or she might put a pharmaceutical drug to an “off label” use, even if the manufacturer, in good faith and with considerable evidence, believes the drug will help. All the while, a third party (say, a researcher) is free to tell the doctor not to use the drug for that purpose.\textsuperscript{155}

Justice Breyer foresaw that the application of the Court’s new “content- and speaker-based” labels to such regulatory rules could have dire ramifications for both the theoretical separation of powers and the practical ability of regulatory agencies to protect

\textsuperscript{150} Id. at 2674.
\textsuperscript{151} \textit{Sorrell}, 131 S. Ct. at 2675; see also Glickman v. Wileman Bros. & Elliott, Inc., 521 U.S. 457, 476 (1997). The \textit{Lochner} era refers to the time when the U.S. Supreme Court issued its opinion in \textit{Lochner v. New York} holding that substantive due process would support striking down state laws that were found to infringe on economic liberty or private contract rights. \textit{Lochner v. New York}, 198 U.S. 45 (1905).
\textsuperscript{152} \textit{Sorrell}, 131 S. Ct. at 2675–76.
\textsuperscript{153} Id. at 2672. The court references 21 U.S.C. §§ 355(b)(1) and 355(d), which mandate testing to ensure drugs are both “safe” and “effective,” as well as the FDA’s “exhaustive regulation of the content of drug labels and the manner in which drugs can be advertised and sold” found in § 352(f)(2) and 21 C.F.R. pts. 201–203. \textit{Id.}
\textsuperscript{154} Id. at 2677 (citing \textit{Va. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.}, 425 U.S. 748, 761, 762 (1976)).
\textsuperscript{155} Id. at 2678 (citing 21 C.F.R. pt. 99; Buckman Co. v. Plaintiffs’ Legal Comm., 531 U.S. 341, 350–51 (2001) (examining the effect of similar regulations applicable to medical devices).
Ultimately, both the Sorrell majority and the dissent acknowledged that the "heightened" level of scrutiny therein applied to commercial speech has important implications for the FDA's current prohibition of off-label marketing. The Second Circuit, seemingly looking to Sorrell for guidance, ordered the parties in United States v. Caronia to brief the First Amendment issue in light of Sorrell. Professor Kevin Outterson, a leading analyst and spokesperson on this issue, speculated that, "In the wake of Sorrell... we can expect the FDA to relax rules against off-label promotion."

The FDA's off-label marketing ban represents a key component of a comprehensive regulatory scheme and provides an important incentive for pharmaceutical companies to continue examining and testing their drugs post-approval in order to demonstrate to the FDA that such substances are safe and effective for additional uses. If products could be marketed off-label without the data to support alternative uses, safety and efficacy could be substantially compromised. According to Kate Greenwood of Seton Hall Law's Center for Health and Pharmaceutical Law and Policy, the current off-label restrictions "serve[ ] as an important prophylactic against false and misleading product promotion... [which] preventive role further distinguishes the ban on off-label promotion from the law invalidated in Sorrell."

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156 Id. at 2678. "If the Court means to create constitutional barriers to regulatory rules that might affect the content of a commercial message, it has embarked upon an unprecedented task - a task that threatens significant judicial interference with widely accepted regulatory activity." Sorrell, 131 S. Ct. at 2678.

157 Id. at 2653, 2678.


159 Kevin Outterson, Incidental Economist, How Should We Buy and Use Efficacy Data on Drugs? (Aug. 1, 2011, 6:09 AM), http://theincidentaleconomist.com/wordpress/how-should-we-buy-and-use-efficacy-data-on-drugs/ (alteration in original). Kevin Outterson served as counsel of record for an amicus brief filed on behalf of the New England Journal of Medicine and three medical organizations supporting Vermont's position in Sorrell before the Supreme Court. See Brief Amici Curiae of the New England Journal of Medicine, the Massachusetts Medical Society, the National Physicians Alliance, and the American Medical Students Association in Support of Petitioners, Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011) (No. 10-779). Ultimately, Professor Outterson contends that the Supreme Court's decision in Sorrell "radically adjusted" the regulatory balance between the FDA and the pharmaceutical industry. Outterson, supra.

160 See Richardson v. Miller, 44 S.W. 3d 1, 12 (2000).

Nevertheless, Sorrell's brand of heightened First Amendment scrutiny provides significant fodder for challenging off-label promotion under circumstances where a pharmaceutical company proposes truthful and non-misleading information about a product. 162

IV. U.S. v. Caronia: The Second Circuit Considers Off-Label Promotion after Sorrell

A. The Sting Operation

November 2, 2005 started like any other day for Alfred Caronia, a pharmaceutical sales representative responsible for promoting Xyrem for Orphan Medical Inc. 163 Caronia had been with Orphan Medical for about eight months and was assigned to a sales territory in New York. 164 He often worked with Dr. Peter Gleason, a licensed psychiatrist with expertise in sleep-related disorders. 165 Gleason was paid thousands of dollars by Orphan to give talks, present at continuing medical education programs, and meet individually with physicians to promote Xyrem, allegedly off-


165 Dr. Gleason's specialty included sleep disorders such as narcolepsy, which refers to the brain's inability to regulate sleep-wake cycles, and cataplexy, which refers to an abrupt temporary loss of voluntary muscular function and tone. Key Sleep Disorders, CENTERS FOR DISEASE CONTROL & PREVENTION, www.cdc.gov/sleep/about_sleep/key_disorders.htm (last visited Nov. 16, 2013).
The day's agenda included a pharmaceutical detailing visit to the office of Dr. Steven Charno. Caronia and Gleason knew Dr. Charno as an internist in Caronia's sales territory who had an interest in off-label uses of Xyrem. In reality, Dr. Charno was a confidential government informant. Unbeknownst to Caronia and Gleason, the scheduled office visit was a sting operation. Undercover governmental officials included special agents from the Federal Bureau of Investigation, U.S. Department of Health and Human Services, and the FDA who were secretly recording the meeting. Gleason carried the conversation with occasional input from Caronia, explaining that Xyrem could treat fibromyalgia, rheumatism, and excessive daytime sleepiness, but also acknowledged that "right now the indication is for narcolepsy." Gleason reported that Xyrem had been used successfully in patients as young as four years and as old as 80. Gleason further instructed Dr. Charno to fill out prescriptions omitting the

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166 Superseding Indictment at 2, 5-6, United States v. Caronia, 576 F. Supp. 2d 385 (E.D.N.Y. July 25, 2007) (No. 06-CR-229). These meetings spanned from 2003 to 2006 and included speaking engagements, dinner events, and meetings where Gleason would, with and without Caronia, promote Xyrem for off-label indications and advise physicians how to conceal these off-label prescriptions from health insurers. Id. at 10-12.

167 Brief and Special Appendix for the United States at 13 & n.10, United States v. Caronia, 703 F.3d 149 (2nd Cir. Oct. 8, 2010) (No. 09-5006-CR). Dr. Charno, a confidential government informant, cooperated with the government against Caronia after pleading guilty to medical insurance fraud for filing $821,000 in fraudulent insurance bills. Id.

168 Xyrem is a powerful, Schedule III central nervous system depressant that carries a "black box" warning because it has potential serious side effects such as difficulty breathing while asleep, abnormal thinking, and depression. See Erika Kelton, Off-Label Pharma Prosecutions Won't Be Silenced By First Amendment Decision, FORBES (Jan. 4, 2013), http://www.forbes.com/sites/eriakelton/2013/01/04/off-label-pharma-prosecutions-wont-be-silenced-by-first-amendment-decision/. In November 2005, just a few days after Caronia and Gleason's visit to Charno's office, Xyrem was approved by the FDA for use in the treatment of excessive daytime sleepiness. See LaSalle, supra note 158, at 868.

169 Brief and Appendix for Defendant-Appellant Alfred Caronia at 3, United States v. Caronia, 703 F.3d 149 (2nd Cir. Apr. 15, 2010) (No. 09-5006).


172 Id. at 13.

173 Brief and Special Appendix for the United States at 22, United States v. Caronia, 703 F.3d 149 (2d Cir. 2010) (No. 09-5006-CR).
diagnosis and diagnosis code so that unsuspecting health insurers would cover his patients’ off-label Xyrem prescriptions.\textsuperscript{174}

Following the sting, Gleason and Caronia were indicted by a federal grand jury and charged with several counts relating to off-label promotion of pharmaceuticals.\textsuperscript{175} Orphan Medical was also charged with one count of introducing a misbranded drug into interstate commerce with intent to defraud and mislead in the marketing of Xyrem. Orphan pled guilty and paid more than $17 million in restitution, criminal fines, and costs.\textsuperscript{176} Eventually, Gleason also pled guilty to a misdemeanor charge of conduct that amounted to introducing a misbranded drug into interstate commerce.\textsuperscript{177}

\textsuperscript{174} Id. at 18-19.

\textsuperscript{175} Superseding Indictment at ¶ 4, United States v. Gleason, Cr. No. 06-229 (S-1) (ENV) (July 25, 2007) [hereinafter Superseding Indictment]; Brief and Special Appendix for the United States at 3-4, United States v. Caronia, 703 F.3d 149 (2nd Cir. 2010) (No. 09-5006-CR). Both men were charged with four counts: introduction of a misbranded drug within the meaning of 21 U.S.C. § 352(f) into interstate commerce in violation of 21 U.S.C. §§ 331(a) & 333(a)(2); conspiracy to introduce a misbranded drug within the meaning of 21 U.S.C. § 352(f) into interstate commerce and to make false statements in violation of 21 U.S.C. §§ 331(a) & 333(a)(2); health care fraud in violation of 18 U.S.C §§ 1349 & 3551; and health care fraud conspiracy in violation of 18 U.S.C. §§ 1349 & 3551. If convicted on all four counts, Caronia and Gleason each could face a sentence of up to 28 years imprisonment, fines of up to $1 million, and forfeiture of any proceeds resulting from the offenses. Superseding Indictment, supra at ¶22–32.


\textsuperscript{177} Administrative Complaint before the Fla. Bd. of Med., at ¶ 9-10, Dep’t of Health v. Gleason, Case No. 2009-18280 (July 11, 2011), available at http://www.psychsearch.net/pdf/2009-18280.pdf. The plea, entered before U.S. Magistrate Judge Cheryl L. Pollak, lasted for 21 minutes and consisted of Gleason entering a guilty plea to only the misdemeanor. Press Release, U.S. Attorney’s Office, E. Dist. of N.Y., Psychiatrist Charged with Conspiracy to Illegally Market the Prescription Medication Xyrem, Also Known as “GHB,” for Unapproved Medical Uses on Behalf of its Manufacturer (Apr. 5, 2006), available at http://www.justice.gov/usao/nye/pr/2006/2006apr05.html. The indictment and plea were not without collateral consequences: Gleason lost his job at a Maryland hospital and has been left to “filling in” at various hospitals. Alex Berenson, Indictment of Doctor Tests Drug Marketing Rules, N.Y. TIMES (July 22, 2006), http://www.nytimes.com/2006/07/22/business/22drugdoc.html?pagewanted=all&_r=0. In June 2008, the Maryland Board of Physicians placed Gleason’s medical license on probation for six months and required him to complete courses in medical records and psychopharmacology for children and adolescents after finding that Gleason regularly prescribed medications without noting their side effects or a patient's responses to the medication and that he kept “scant” notes of his treatment in the patient's records. Cal. Physician's & Surgeon's Certificate at ¶ 9, In re: Gleason, No. G87635, Case No. 16-2008-192888. In March 2010, the Medical Board of California publically reprimanded Gleason and required him to complete educational courses on medical records documentation and prescribing practices based on the conduct in the Maryland complaint. Id. In October 2010, the Pennsylvania Board of Medicine suspended Gleason’s license for one year for failing to disclose his conviction on his
B. The District Court’s Opinion in United States v. Caronia

The District Court for the Eastern District of New York noted the limited FDA-approved uses of Xyrem: "serious potential side effects" associated with the use of Xyrem, and a "black box" warning relating to potential abuse, overdose, and dependence on Xyrem. It also considered several provisions of the FDCA regarding off-label uses and misbranding of FDA-approved drugs.

As a preliminary matter, the district court disposed of Caronia's statutory arguments that Xyrem had not been held for sale after shipment in interstate commerce within the meaning of 21 U.S.C. § 331(k), and considered whether Caronia misbranded Xyrem within the meaning of 21 U.S.C. § 352(f).

Caronia made three related arguments regarding this issue. Caronia, 576 F. Supp. at 391–92. First, he contended that the same method of administration and dosage was used regardless of whether Xyrem was prescribed on or off-label and that, since the potential dangers were the same, he satisfied his duty to provide adequate directions when he gave Charno the black box warning. Id. at 391–92. The judge found this argument to be "utterly without merit" since the FDA’s regulations prohibit off-label marketing regardless of what warnings are given. Id. at 392. Indeed, the court wrote, "if, as the manufacturer's representative, Caronia promoted Xyrem for off-label uses, whatever information (accurate or inaccurate) Caronia may have provided in the course of the promotion of those off-label uses is irrelevant to a misbranding charge." Id. Caronia then argued that the warnings were unnecessary because Charno was only a confidential
addressed the alleged constitutional infirmity of the misbranding charges.\(^1\) In particular, Caronia argued that, "the government cannot restrict truthful, non-misleading promotion by a pharmaceutical manufacturer (or its employees) to a physician of the off-label uses of an FDA-approved drug."\(^2\) Thus, according to Caronia, the misbranding provisions of the FDCA impermissibly restricted his First Amendment commercial speech rights.\(^3\) The government countered that the First Amendment did not apply to Caronia's conduct and that, even if it had applied, the FDCA's restrictions on promotion of off-label uses were constitutionally sound.\(^4\) The district court acknowledged that Caronia’s “constitutional attack call[ed] into question America’s regulatory regime for the approval and marketing of prescription drugs.”\(^5\) Basing his argument on *United States v. Caputo*\(^6\) and *Washington Legal Foundation v. Henney*,\(^7\) as well as government informant and was not going to be an actual prescriber or user of the drug. *Id.* The court was not persuaded by this argument either, finding that pursuant to the statute, “[i]t is the mouth of the promoter not the ear or intent of the audience that controls.” *Id.* In Caronia's final statutory argument, he alleged that, as a matter of fact, he did not promote Xyrem for its off-label uses. *Caronia*, 576 F. Supp. 2d at 393. The court, however, declined to consider this argument, noting that factual disputes “are resolved by trial not motion.” *Id.*

\(^{1}\) 21 U.S.C. § 352(f) (2012). This statute provides that:

> A drug or device shall be deemed to be misbranded . . . (f) unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users . . . .

*Id.*

\(^{2}\) *Caronia*, 576 F. Supp. 2d at 393.

\(^{3}\) *Id.*

\(^{4}\) *Id.*

\(^{5}\) *Id.*

\(^{6}\) 517 F.3d 935, 936 (7th Cir. 2008). In *Caputo*, defendants Ross Caputo and his assistant, Robert Riley, were charged with conspiring to defraud the United States, mail fraud, wire fraud, lying to federal agents, and the delivery of misbranded devices in connection with the sale of a new type of autoclave for purposes not approved by the FDA. *Id.* at 938. After the jury convicted both defendants, the judge sentenced Caputo to 10 years imprisonment, sentenced Riley to six years imprisonment, and ordered both to make restitution of $17.2 million (the total sale price of all autoclave units ever sold). *Id.* Caputo and Riley appealed, arguing primarily that the FDCA violated their First Amendment rights by restricting their promotional materials to only those uses approved by the FDA. *Id.* The Seventh Circuit dodged the question, writing instead that, "we need not decide today whether a seller of drugs or medical devices has a constitutional right to promote off-label uses . . . [because] unless the machine itself could be sold lawfully, there were no lawful off-label uses to promote." *Id.* at 940. Since the jury had found that the autoclave could not be sold lawfully, the promotion of the autoclave was not off-
as FDA Draft Guidance on the use of scientific articles for promotional purposes, Caronia pointed out that despite the FDA's prohibition against off-label promotion by manufacturers, physicians can lawfully prescribe an approved drug for any purpose, whether on- or off-label.\textsuperscript{188} Accordingly, he argued, telling physicians about such off-label uses must also be lawful.\textsuperscript{189} The district court acknowledged the wisdom of \textit{Caputo} and \textit{Henney}, but concluded that the issues Caronia raised were "very much unsettled, not only in this circuit but nationwide."\textsuperscript{190}

The initial inquiry for the district court was whether the First Amendment was, in fact, implicated, consistent with the current state of the law.\textsuperscript{191} Contrary to the

case – it was essentially no-label. \textit{Id.} Nevertheless, the court did note in dicta that, in light of recent Supreme Court commercial speech cases, the FDA's off-label provisions may be unconstitutional in some situations. \textit{Caputo}, 517 F.3d at 939.\textsuperscript{187} 202 F.3d 331, 332–33 (D.C. Cir. 2000). In \textit{Henney}, the D.C. Court of Appeals considered the FDA's attempt to regulate, via guidance documents, off-label promotion in the context of dissemination of journal articles and continuing medical education (CME) for physicians. \textit{Id.} at 333. The Washington Legal Foundation brought suit against FDA Commissioner Jane E. Henney and U.S. Department of Health and Human Services Secretary Donna E. Shalala, alleging that the FDA guidance documents violated its physician members' First Amendment right to receive information regarding off-label uses. \textit{Id.} at 333–34. The district court determined that the FDA guidance documents regulated commercial speech and then applied the \textit{Central Hudson} test to determine whether the restrictions were constitutional. \textit{Id.} at 334. After finding that the speech concerned lawful activity and was not misleading, and that restricting off-label promotion "advanced the government's substantial interest in encouraging manufacturers to seek FDA approval for off-label uses," the district court found that the guidance documents nevertheless regulated more speech than necessary to accomplish this objective. \textit{Id.} As a result, the district court enjoined the FDA from prohibiting journal articles or CME, regardless of whether the uses were off-label. \textit{Id.} Not long after, the FDA Modernization Act (FDAMA) took effect, which superseded the guidance documents, but nevertheless contained essentially the same prohibitions. \textit{Henney}, 202 F.3d at 334. In a later opinion, the district court held that the Act's provisions were likewise unconstitutional, and the FDA appealed. \textit{Id.} at 335. At oral argument before the Court of Appeals, however, the government clarified its position, indicating that the provisions were simply a "safe harbor" and that "neither the FDAMA nor the CME Guidance independently authorizes the FDA to prohibit or to sanction speech," thus placing no constitutional issue before the court. \textit{Id.} at 335–36. The appellate court then vacated the district court's decisions and injunctions insofar as they declared the guidance documents and Act unconstitutional. \textit{Id.} at 337.


\textsuperscript{189} Caronia, 576 F. Supp. 2d at 393.

\textsuperscript{190} Id. at 393–94.

\textsuperscript{191} Id. at 395. The district court looked to dicta in \textit{Henney}, which left open the opportunity for a
government's argument, the district court held that Caronia's alleged off-label promotion did constitute speech (not merely conduct) within the scope of First Amendment protection. Applying the standard set forth by the Supreme Court in *Bolger v. Young Drug Products Corp.*, the district court addressed whether Caronia's off-label promotion was entitled to protection as commercial speech. Following the analysis applied in *Washington Legal Foundation v. Friedman*, the district court found that, "regardless what else might have been covered in his discussions, Caronia's alleged speech was made on behalf of the manufacturer and clearly (1) encouraged physicians to prescribe Xyrem, (2) referred to a specific product, and (3) was economically motivated." As a result, the district court found that promotion of off-label uses of Xyrem was "entitled to the qualified but nonetheless substantial protection accorded to commercial speech."

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193 *Bolger v. Young Drug Products Corp.*, 463 U.S. 60, 66–68 (1983). As the district court noted, in applying the *Bolger* test, a court must examine: "(1) whether the expression is an advertisement; (2) whether it refers to a specific product; [and] (3) whether the speaker has an economic motivation for speaking." *Caronia*, 576 F. Supp. 2d at 396. As noted previously, Caronia adopted Gleason's First Amendment arguments from his motion to dismiss. See *id.* at 395. Importantly, however, Gleason argued that his off-label promotion amounted to pure speech, since he was a doctor merely "expressing his opinions about a drug he could and did prescribe." *Id.* at 395. Thus, Gleason argued, his speech was "scientific and academic speech, which resides at the core of the First Amendment and, therefore, should receive the highest constitutional protection." *Id.* Since Caronia was only a sales representative, the court suggested that this argument would have been unavailable to him, and instead noted that Caronia adopted Gleason's alternative argument that his off-label promotions were nevertheless protected as commercial speech. *Id.* at 396.

194 *Id.* at 395 (citing *Bolger*, 463 U.S. at 68).
Having found that Caronia’s promotional activities constituted commercial speech, the district court applied the Central Hudson test to determine whether the speech was protected by the First Amendment. As to the first Central Hudson prong, requiring that the speech be lawful and not misleading, the district court concluded that Caronia could not be found to have promoted unlawful activity since “[t]he proper inquiry is not whether the speech violates a law or a regulation, but whether the conduct that the speech promotes violates the law.” Because Caronia’s speech promoted the lawful activity of prescribing off-label uses of Xyrem, the conduct he promoted was lawful. Nor did the district court find that Caronia’s promotion of Xyrem off-label was inherently misleading, since Caronia never claimed the FDA had approved the off-label uses.

As for the second prong of the Central Hudson analysis, the district court in Caronia found that the government had a “substantial interest in subjecting off-label uses of a drug or medical device to the FDA’s evaluation process.” The district court summarily addressed the third prong of Central Hudson (requiring that the regulation directly advance a governmental interest) by emphasizing the lack of incentive for manufacturers to seek FDA approval of off-label uses absent restrictions on off-label promotion. As the court had noted in Friedman:

It is clear that manufacturers have incentives to circumvent approval requirements, but one wonders what incentives they have to obtain

197 Id. at 396–402. See supra note 127 and accompanying text (discussing Central Hudson test).
198 Caronia, 576 F. Supp. 2d at 397 (citing Friedman, 13 F. Supp. 2d at 66).
199 Id.
200 Id. at 397-98. Rather, the district court adopted the holding from United States v. Caputo, concluding that:

[Caronia’s] 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, at this stage of the proceedings, that [defendant’s] speech was inherently misleading.

Id. (quoting United States v. Caputo, 288 F. Supp. 2d 912, 921 (N.D. Ill. 2003)). Indeed, the district court echoed Friedman’s particularly harsh sentiment that, “In asserting that any and all claims about the safety, effectiveness, contraindications, side effects[,] and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.” Id. at 397 (quoting Friedman, 13 F. Supp. 2d at 67).
201 Id. at 398.
202 Id.
them? For a brand-new drug, the incentive is simple: the pharmaceutical company cannot manufacture or introduce the drug into interstate commerce without FDA approval. However, the drugs subject to off-label prescriptions are *already* in interstate commerce, so the obvious restriction on conduct is unavailable. Therefore, one of the few mechanisms available to FDA to compel manufacturer behavior is to constrain their marketing options; i.e. control the labeling, advertising, and marketing.  

With respect to the third *Central Hudson* prong, the district court in *Caronia* found the FDA’s restrictions on commercial speech “directly advance[d] the government’s interest in subjecting off-label uses of a drug like Xyrem to the FDA’s evaluation process.”  

Although the district court found that *Friedman* provided appropriate guidance up to this point, the analysis diverged once the court came to the fourth *Central Hudson* prong, which required the government to establish that the FDA’s restrictions on pharmaceutical manufacturers’ off-label promotions were no more extensive than necessary. Indeed, while the *Friedman* court found that the FDA’s guidance documents regarding manufacturer sponsorship of CME and provision of peer-reviewed articles with a focus on off-label uses were unconstitutional because they were more extensive than necessary, the district court in *Caronia* noted that the less restrictive alternatives proposed in *Friedman* anticipated the very case brought by the government in *Caronia*. Instead, the district court in *Caronia* acknowledged the lower court’s recognition in *Caputo* that challenging the statutory misbranding provisions of the FDCA “strikes at the very heart of the FDA’s ability to proscribe manufacturer promotion of off-label uses.” The court also found there are no less burdensome alternatives to those provisions that would advance the government’s substantial

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203 Id. (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998)). *Friedman* concerned the procedures established under FDAMA for drug and device manufacturers to disseminate information concerning off-label uses. *Friedman*, 13 F. Supp. 2d at 72. The district court issued an injunction, finding a likelihood of success on the argument that the statutory provision violated the First Amendment. *Id.* at 72. The government appealed and the appellate court disagreed, dismissing the appeal and vacating the injunction. *Id.*

204 *Caronia*, 576 F. Supp. at 397.

205 *Id.* at 402.

206 *Id.* In *Washington Legal Foundation v. Friedman*, the court had reasoned that, “even though the FDA guidance documents were themselves unconstitutional, there remained adequate incentives to compel manufacturers to get off-label uses approved. . . . For instance, the FDCA would still prohibit . . . initiation of person-to-person-contact with a doctor about off-label use . . . .” *Caronia*, 576 F. Supp. 2d at 399 (citing Wash. Legal Found. v. Friedman, 13 F. Supp. 2d at 73). This alternative, however, was precisely the conduct with which Caronia was charged. *Id.* at 401.

207 *Id.* at 399.
interests. As to the dicta in the Seventh Circuit Caputo case implying that, at least in some circumstances, forbidding manufacturers to promote off-label uses was unconstitutional, the district court in Caronia instead relied on the Seventh Circuit's prior “balancing” criteria. Specifically, the court would have weighed permitting pharmaceutical manufacturers to speak freely about any of the drug's uses against the FDA's ability to withhold approval of otherwise beneficial drugs because of the drug's other “questionable” off-label uses.

Thus, the district court resolved that “constraining the marketing options of manufacturers is one of the 'few mechanisms available' to the FDA to ensure that manufacturers will not seek approval for certain limited uses of drugs, then promote that same drug for off-label uses, effectively circumventing the FDA's new drug requirements.” In drawing this conclusion, the district court took notice of the Seventh Circuit's caution that, “[a] court should hesitate before extending . . . [a] historical reading of the Constitution in a way that injures the very audience that is supposed to benefit from free speech.”

Noting that the Seventh Circuit was unable to identify a less restrictive manner by which to prohibit pharmaceutical companies from circumventing the FDA approval process, the district court found that the FDCA provisions passed constitutional muster. Indeed, the court held, “[a]ny right Caronia had as Xyrem's sales representative to express as commercial speech the truthful promotion of Xyrem's off-label uses is not unconstitutionally restricted by the misbranding provisions of the FDCA.” Accordingly, the district court denied Caronia's motion in its entirety, and ultimately, Caronia was convicted on one count of “conspiracy to introduce or deliver

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208 Id.
210 Caronia, 576 F. Supp. 2d at 400 (citing Caputo, 517 F.3d at 940).
211 Id. at 401 (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998)).
212 Id. at 400 (quoting United States v. Caputo, 517 F.3d 935, 939 (7th Cir. 2008)). The district court elaborated that, “unlike in Western States, where neither logic nor the government had explained why restricting advertising was a 'necessary as opposed to merely convenient’ way to achieve its ends, here, the FDA's maintaining through the FDCA’s misbranding provisions some control over the off-label promotion of manufacturers does appear essential to maintaining the integrity of the FDA's new drug approval process.” Id. at 401.
213 Id. at 402.
214 Id.
for introduction to interstate commerce a drug, Xyrem, that was misbranded.”

C. The Second Circuit Court of Appeals: Oral Argument

Following his conviction, Caronia appealed on both procedural and substantive grounds alleging that the FDA’s restriction on off-label promotion of pharmaceutical products violated his First Amendment commercial speech rights. The Washington Legal Foundation filed an amicus brief in support of Caronia’s assertions. At oral argument, the Washington Legal Foundation argued that the FDA’s regulation was overbroad as “the government didn’t need to restrict Caronia’s speech in order to serve any compelling interest” in incentivizing manufacturers to utilize the drug approval process. In response to the Second Circuit’s concern about uninformed salesmen with an incentive to sell the drug, counsel for Caronia suggested that the government can counter fraudulent or misleading claims on a case-by-case basis, rather than restricting all truthful, non-misleading information put forward by salesmen.

Defending the government’s position, the DOJ argued that promotion of off-label uses is not the crime; rather, the crime is the introduction of the misbranded drug into interstate commerce. The DOJ asserted that the off-label promotion is simply evidence of the intent to introduce that drug into interstate commerce. The DOJ relied on the Supreme Court case Wisconsin v. Mitchell, where the Court held that using speech as an element of a crime was not a First Amendment violation.

215 Brief and Appendix for Defendant-Appellant Alfred Caronia at 15, United States v. Caronia, No. 09-5006-cr(L) (2d Cir. Apr. 16, 2010). After the verdict was announced, Caronia orally moved for a judgment of acquittal pursuant to Fed. R. Crim. P. 29(c)(1) based on the split verdict finding Caronia guilty of conspiracy but not the underlying misbranding charge, as well as the lack of evidence presented at trial. Id. at 14–15. Judge Eric Vitaliano denied Caronia’s motion for acquittal on December 12, 2008. Id. at 1.

216 See Brief and Appendix for Defendant-Appellant Alfred Caronia, United States v. Caronia, No. 09-5006-cr(L) (2d Cir. Apr. 16, 2010).


218 Unofficial Oral Argument Transcript at 3-4, United States v. Caronia, No. 09-5006-cr(L) (Dec. 2, 2010), available at http://druganddevicelaw.net/Caronia%202d%20Transcript.pdf. Judge Reena Raggi of the Second Circuit later clarified that, in fact, the issue is not over breadth of the provisions, but rather whether the provisions are narrowly tailored pursuant to the fourth prong of the Central Hudson analysis. Id. at 9.

219 Id. at 5.

220 Id. at 6.

221 Id.

222 Wisconsin v. Mitchell, 508 U.S. 476 (1993). See also Unofficial Oral Argument Transcript,
The Second Circuit also inquired about why a physician could prescribe a drug and order it from the pharmacy for any purpose, but it was illegal for a salesman to promote the same. The DOJ responded that the salesman could promote it legally, but not introduce it into interstate commerce because the label “didn’t provide enough speech” or adequate instructions for alternate uses. When prompted as to whether there were any less restrictive alternatives, such as setting timelines for approval of off-label uses, DOJ cited to past “public health disasters” as a result of off-label drug use.

The Second Circuit also probed the issue of whether the FDA provisions should prevent doctors like Gleason, nationally renowned for his research on Xyrem, from sharing his knowledge regarding the drug solely on the basis that he was on Orphan Medical’s payroll. Addressing the impropriety of a prohibition against “hired guns” speaking about company products, counsel for Caronia maintained that such a limitation thwarts research into off-label uses because it is the revenue from the drug sales that supports new research. The Second Circuit, unpersuaded by this assertion, noted that nothing supporting such an assertion was contained in the record.

D. The Second Circuit's Decision in United States v. Caronia: Analysis of Majority Opinion

Nearly two years after oral argument, in December, 2012 a three-judge panel of the Second Circuit rendered its decision in Caronia, ultimately vacating Caronia’s conviction and remanding the matter to the district court. The majority, consisting of Judges Chin and Raggi, rejected the government’s argument that it had used Caronia’s off-label promotion as evidence of Xyrem’s intended uses and held that, in fact, the government had prosecuted Caronia simply on the basis of his speech. Relying heavily on Sorrell, the majority went on to further conclude that the government’s theory of prosecution ran afoul of the First Amendment because it: (1) imposed “content-” and “speaker”-based burdens on speech, and (2) failed to satisfy even the intermediate scrutiny standards established under Central Hudson. Notably, the majority took care

\[supra\] note 224, at 10.
223 Unofficial Oral Argument Transcript, supra note 217 at 7.
224 Id. at 7-8.
225 Id. at 12-13.
226 Id. at 15.
227 Id.
228 Unofficial Oral Argument Transcript supra note 224, at 15.
229 United States v. Caronia, 703 F.3d 149, 152 (2d Cir. 2012).
230 Id. at 152, 161.
231 Id. at 164.
to note that, pursuant to the principle of constitutional avoidance, its decision rested upon a reading of the FDCA that does not criminalize the act of off-label promotion itself, "because such a construction—and a conviction obtained under the government's application of the FDCA—would run afoul of the First Amendment."232

The Second Circuit majority found that the government was not entitled to the benefit of Mitchell because it had prosecuted Caronia solely for his speech, rather than relying on that speech as evidence of Xyrem's intended uses and, thus, mislabeling for that intended use.233 Specifically, the majority highlighted the government's conduct and repeated arguments at trial suggesting that Caronia could be found criminally liable based on his off-label promotional activities alone, as well as the government's failure to suggest "that Caronia engaged in any form of misbranding other than the promotion of the off-label use of an FDA-approved drug."234 Moreover, the majority felt that the district court's instruction, when combined with the government's presentation, "left the jury to understand that Caronia's speech was itself the proscribed conduct."235 Because the government had incontrovertibly prosecuted Caronia for his "speech in aid of pharmaceutical marketing"—a category of expression protected under Sorrell—the majority found the government's evidence-of-intent argument lacked any merit.236 Importantly, the majority did not shut the door on the government's use of off-label promotion as evidence of intent in future cases, holding simply that the prosecution of Caronia had not proceeded in that fashion and thus was not exempt from First Amendment scrutiny.237

Having dispensed with the government's evidence-of-intent argument, the

232 Id. at 162. Accordingly, the Second Circuit majority emphasized that it was reversing Caronia's conviction "for narrower reasons than he urges." Id. at 160.
233 Id. at 161. See Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993). In Mitchell, the Supreme Court held that using speech as an element of a crime did not violate principles of the First Amendment. Id.
234 Caronia, 703 F.3d at 160-61.
235 Id. at 161. The district court instructed the jury that off-label promotion of a drug by a pharmaceutical representative may constitute misbranding and is prohibited. Id. at 158-59, 161.
236 Id. at 162. "Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment . . . the creation and dissemination of information are speech within the meaning of the First Amendment." Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2659, 2667 (2011).
237 Caronia, 703 F.3d at 161-62. At the same time, the Second Circuit majority expressed skepticism as to how the government would draw the line, when using speech as evidence of intent, between misbranding worthy of criminal sanctions and permissible "communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use." Id. at 162 n.9.
majority then turned to whether prosecuting Caronia under the FDCA’s misbranding provisions based on his promotion of Xyrem for non-FDA-approved uses was permissible under the First Amendment.\textsuperscript{238} Applying the two-step analysis embodied in \textit{Sorrell}, the majority first observed that the government’s theory of prosecution against Caronia, namely that the FDCA criminalizes off-label promotion by drug manufacturers, was both “content”- and “speaker”-based, and therefore warranted heightened scrutiny.\textsuperscript{239} As to content, the government’s construction of the FDCA permitted speech about FDA-approved drug uses, while proscribing speech about off-label uses (even though the off-label uses were themselves legal).\textsuperscript{240}

As to the identity of the speaker, the majority emphasized that the government’s construction of the FDCA targeted pharmaceutical manufacturers while permitting “physicians and academics, for example, to speak about off-label use without consequence.”\textsuperscript{241} Additionally, the Second Circuit majority added that Caronia’s claim to First Amendment protection was more compelling than that of the pharmaceutical manufacturers and data-mining companies in \textit{Sorrell}, given that violations of the FDCA result in criminal penalties.\textsuperscript{242}

Turning to the second step of the \textit{Sorrell} inquiry, the Second Circuit majority considered whether the government’s construction of the FDCA survived intermediate scrutiny under \textit{Central Hudson}.\textsuperscript{243} As an initial matter, the majority noted that off-label drug use was an entirely lawful activity, and that promotion thereof was not inherently false or misleading.\textsuperscript{244} Had the government contended that Caronia’s promotional speech was false or misleading, First Amendment protections would not have attached, and prosecution under 21 U.S.C. § 331(a) would have been entirely appropriate.\textsuperscript{245} With regard to the second prong of \textit{Central Hudson} analysis, the majority accepted that the government had a substantial interest in “preserving the effectiveness and integrity of

\textsuperscript{238} Id. at 162.
\textsuperscript{239} Id. at 163-65. At the outset, the majority recognized that, while the U.S. Supreme Court had not resolved whether strict scrutiny, intermediate scrutiny, or some other form of heightened scrutiny should be used to assess restrictions on speech in aid of pharmaceutical marketing, “the outcome [would be] the same whether a special commercial speech inquiry or a stricter form of judicial scrutiny [was] applied.” Id. at 164 (quoting \textit{Sorrell}, 131 S. Ct. at 2667).
\textsuperscript{240} Id. at 165.
\textsuperscript{241} \textit{Caronia}, 703 F.3d at 165.
\textsuperscript{242} Id. at 163, 165 (citing Holder v. Humanitarian Law Project, 130 S. Ct. 2705, 2724 (2010)).
\textsuperscript{243} Id. at 165-66.
\textsuperscript{244} Id. at 165.
\textsuperscript{245} Id. at 165-66 n.10. The government did not argue that Caronia’s promotional speech was false or misleading. Id.
the FDA’s drug approval process, and . . . in reducing patient exposure to unsafe and ineffective drugs.” However, the majority determined that the government was unable to satisfy the third and fourth prongs of the Central Hudson test.

According to the Second Circuit majority, the government’s reading of the FDCA did not directly advance its interest in safeguarding the role of the FDA’s drug-approval process because, regardless of the prohibition against off-label promotion, physicians could still prescribe and patients could still use drugs for unapproved purposes. Moreover, as the majority saw it, “prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use ‘paternalistically’ interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public’s detriment, informed and intelligent treatment decisions.” In fact, the majority concluded that the government had recognized the value of free-flowing information regarding off-label uses of FDA-approved drugs when it created a safe harbor permitting the dissemination of such information through scientific journals and continuing medical education programs. Ultimately, the majority reasoned, “criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably ineffective means to achieve” the government’s goal of encouraging physicians to prescribe drugs only for FDA-approved purposes.

Additionally, in the eyes of the Second Circuit majority, the government’s construction of the FDCA was not narrowly drawn, considering the government had several less restrictive alternatives of protected expression at its disposal. For example, the government could provide information to help prescribers and consumers differentiate false and misleading messages from truthful and accurate ones, develop a

246 *Caronia*, 703 F.3d at 166 (citing *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000)).
247 *Id.* Specifically, the Government was unable to prove that its construction of the FDCA directly advanced the government’s interests and that the regulation was narrowly drawn, respectively. *Id.*
248 *Id.* at 166 (citing *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2668–69 (2011)).
250 United States v. Caronia, at 167 (citing *Wash. Legal Found. v. Henney*, 202 F.3d 331, 335 (D.C. Cir. 2000)).
252 *Id.* at 48.
warning or disclaimer system, or create safety tiers to distinguish between various drugs in the off-label market.\textsuperscript{253} Moreover, the FDA could require drug companies to list any existing or intended indications for a drug when they apply for FDA approval, thereby permitting interested parties to track the drug’s evolution.\textsuperscript{254} In order to reduce off-label use, the government could also cap the number of permissible off-label prescriptions or prohibit particularly dangerous off-label uses altogether.\textsuperscript{255} For its part, the government contended that none of the court’s suggested alternatives would be administrable, feasible, or effective ways to preserve the integrity of the FDA’s drug-approval process or protect patients from unsafe, untested drugs.\textsuperscript{256} The majority, however, ruled that, “such conclusory assertions are insufficient to sustain the government’s burden of demonstrating that the proposed alternatives are less effective than its proposed construction of the FDCA in furthering the governmental interests identified.”\textsuperscript{257}

E. The Second Circuit’s Decision in \textit{United States v. Caronia}: Analysis of Dissenting Opinion

In her dissent, Judge Debra Ann Livingston took the majority to task for “call[ing] into question the very foundations of our century-old system of drug regulation”—a result not compelled by U.S. Supreme Court precedent.\textsuperscript{258} Judge Livingston would have upheld Caronia’s conviction on grounds that: (1) the government permissibly used Caronia’s off-label promotion as evidence of motive or intent, not as the stand-alone basis for his conviction; and (2) even if the First Amendment did apply to this case, the government’s construction of the FDCA fulfilled the requirements of \textit{Central Hudson}.\textsuperscript{259}

As Judge Livingston viewed it, Caronia was neither prosecuted nor convicted merely for his speech, because, as even the majority recognized, \textit{Mitchell} contemplates that off-label promotion could be used for purposes of establishing intent to introduce a misbranded drug into interstate commerce.\textsuperscript{260} Judge Livingston further noted that the district court’s jury instruction, read in its totality, apprised the jury of all the essential elements of conspiracy and misbranding, and made clear that they needed to find each

\textsuperscript{253} \textit{Id.}
\textsuperscript{254} \textit{Id.} at 48–49.
\textsuperscript{255} \textit{Id.} at 49–50.
\textsuperscript{256} \textit{Id.} at 50.
\textsuperscript{257} \textit{United States v. Caronia}, 703 F.3d 149, 150 (2012).
\textsuperscript{258} \textit{Id.} at 169 (Livingston, J., dissenting).
\textsuperscript{259} \textit{Id.} at 177 (Livingston, J., dissenting).
\textsuperscript{260} \textit{Id.} at 177–78 (Livingston, J., dissenting). \textit{See supra} note 233 and accompanying text (discussing Supreme Court’s holding in \textit{Mitchell}).
element proven beyond a reasonable doubt. The portion upon which the majority focused did not encourage the jury to convict Caronia for his speech, but rather provided an appropriate standard for the jury to use in evaluating whether there was "an objective intent that [Xyrem] be used for off-label purposes — and thus that it [was] being placed into interstate commerce without proper labeling." As Judge Livingston pointed out, not even Caronia had objected to the jury charge or, for that matter, to the prosecution's references in its summation to of Caronia's off-label promotional activities. More importantly, Judge Livingston observed that the First Amendment has never barred the use of speech to demonstrate that otherwise lawful conduct was impermissible when undertaken with a prohibited motive. Additionally, FDCA's declining to prohibit off-label uses was not dispositive of Caronia's First Amendment claim, since, as Judge Livingston pointed out, "speech encouraging others to engage in certain legal conduct has long been directly regulated or prohibited in a variety of areas." Finally, Judge Livingston emphasized that the principal cases relied upon by the majority involved statutes that directly regulated speech, rather than simply permitting speech to be used as evidence of intent.

At base, Judge Livingston

261 Id. at 181-82 (Livingston, J., dissenting):

How do you find the defendant, ALFRED CARONIA, on Count One of the Information? (a) Conspiracy to introduce or deliver for introduction into interstate commerce a drug, Xyrem, that was misbranded? NOT GUILTY ______ GUILTY ______ and (b) Conspiracy to do an act with respect to a drug, Xyrem, when such drug was held for sale after shipment in interstate commerce when such act would result in Xyrem being misbranded? NOT GUILTY____ / GUILTY ____. The jury concluded that Caronia was guilty with respect to question (a) and not guilty with respect to question (b).

262 Caronia, 703 F.3d at 173.

263 Id. at 173 n.4 (explaining Judge Livingston's understanding of the district court's jury instruction).

264 Id., at 175-76. For instance, an aggrieved employee in a Title VII suit may rely on comments made by her employer to demonstrate discriminatory intent without violating that employer's First Amendment rights. See id. at 175 (citing Wisconsin v. Mitchell, 508 U.S. 476, 487-90 (1993)).

265 Id. at 175 n.5 (Livingston, J., dissenting) (emphasis in original). By way of example, Judge Livingston noted the prohibitions against insider trading, discussion of price hikes among rival corporations pursuant to the Sherman Act, non-lawyers providing even sound legal advice, or unlicensed laypersons providing even accurate medical diagnoses. Id.

266 See id. at 176-77 (Livingston, J., dissenting). Judge Livingston explained that, "[A] pharmacy would violate the statute in Western States as soon as it advertised the compounding of particular drugs. . . . Similarly, a Vermont pharmacy would violate the statute in Sorrell as soon as it disseminated prescriber-identifying information for marketing purposes. . . . Speech alone is not, however, sufficient to sustain a conviction under 21 U.S.C. § 331(a)." See id.; supra note 17 and
concluded:

[The]he simple fact that one is generally allowed to sell something does not imbue one with a constitutional right to sell it for any intended purpose. And the prohibition here on distributing drugs with the intent that they be used for purposes not supported by their labeling is entirely consistent with the broader purposes of the FDCA—namely, minimizing those occasions on which patients use drugs that have not been shown to be safe and effective.267

Even if the use of speech as evidence of intent had triggered First Amendment protections, Judge Livingston would have found that the FDCA's misbranding provision satisfied the heightened scrutiny required under both Central Hudson and Sorrel.268 In particular, Judge Livingston concluded that the FDCA's prohibition of off-label marketing directly advanced the government's substantial interest in preserving the integrity of the FDA drug-approval process, as it represents one of the only mechanisms for incentivizing participation in that regulatory scheme.269 The proscription against off-label promotion's limited application to pharmaceutical manufacturers makes perfect sense, as they are the only entities in a position to undermine the FDA's drug-approval process.270 Judge Livingston suggested that adopting Caronia’s position would undercut the approval process, not only for existing drugs, but also for new drugs, since a drug deemed safe for certain uses might be considered unsafe overall if the FDA had to take into account all the other (unsubstantiated) indications and populations for which a manufacturer could market the product.271 With regard to the fourth Central Hudson prong, Judge Livingston did not find any of the majority's proffered less speech-
restrictive alternatives to be persuasive. Judge Livingston stated that instituting a disclaimer system or requiring manufacturers to list all intended uses of their products would "encourage promotion based on data much less reliable than the clinical investigations," required under the FDCA. Placing a ceiling on the number of off-label prescriptions could result in patients failing to receive the treatments they need because other patients had already been prescribed ineffective or even unsafe ones. As to a ban on off-label prescriptions entirely, Judge Livingston observed that this would "constitute an unprecedented intrusion into the practice of medicine, and would result in perhaps an even greater restriction on speech."

In conclusion, Judge Livingston offered that the "content- and speaker-based" nature of the FDCA's off-label marketing prohibition was not remarkable, since all commercial speech cases involve regulations of that variety. Moreover, Sorrell acknowledged that statutes geared toward preventing false or misleading speech are appropriately analyzed under the more deferential standard typically applied to commercial speech.

V. U.S. v. Harkonen: The Ninth Circuit Considers Off-Label Promotion

In U.S. v. Harkonen, the government charged W. Scott Harkonen, M.D. with (1)
wire fraud and (2) misbranding under the FDCA. InterMune, Harkonen’s employer, is the manufacturer of Actimmune, a drug approved to treat severe osteoporosis and related conditions but not approved to treat a separate condition known as idiopathic pulmonary fibrosis (IPF). InterMune conducted a clinical trial, which yielded disappointing results, but when the data was re-evaluated, showed promise for a subset of IPF patients who started treatment at a less advanced stage. Based on these results, Harkonen sent out a press release declaring this finding to physicians and patients. He also assisted a specialty pharmacy in Florida with a press release and letter to patients and doctors describing the “preliminary data” and encouraging use of Actimmune to treat IPF. Sales representatives were also provided with T-shirts to promote the use of Actimmune.

After the clinical trial’s disappointing results concerning demonstrated benefit to patients, Phase II of the trial was discontinued. Several months later, the DOJ indicted Harkonen for disseminating information about Actimmune for the treatment of IPF with the intent to defraud and mislead. In off-label terms, Actimmune was “misbranded.”

Harkonen moved to dismiss the charges on the basis that the press release and other communications about Actimmune’s effectiveness for treating IPF, which were labeled “disseminations,” should have been excluded from evidence because they did not constitute impermissible “labeling” within the meaning of the FDCA. Further, the releases and communications were arguably protected under the First Amendment. Harkonen was convicted only of “wire fraud” and was acquitted on charges of off-label promotion. On appeal to the Ninth Circuit, he argued that his

279 Harkonen, No. C 08-00164 MHP, at 1.
280 Id. at 2.
281 Id. at 2-3.
282 Id. at 3.
283 Id. at 2.
284 Id. at 2.
286 See id.
287 Id. at 3-4.
288 Id. at 5.
conviction should be reversed because the news release “expressed a scientific view” that was protected speech under the First Amendment.290 He further argued that his ability to “truthfully summarize results of a clinical trial” was protected by the First Amendment because “decisions about prescribing medicine ‘must result from free and uninhibited speech.’”291 The government responded that the First Amendment does not bar a “criminal prosecution of false statements with an intent to defraud” just because they “concern scientific matters.”292 Ultimately, the government’s position prevailed.293 Summarily dismissing Harkonen’s First Amendment argument in a ruling issued on March 4, 2013, the appellate court found no basis for disturbing the jury’s conclusion, beyond a reasonable doubt, that Harkonen had issued the press release with the specific intent to defraud, thereby placing the speech beyond the ambit of First Amendment protection.294

VI. Implications of U.S. v. Caronia and U.S. v. Harkonen on FDA Policy

In holding that the FDA prohibition on off-label marketing is unconstitutional, the Caronia majority effectively dismissed the government’s contention that FDA regulations prohibiting off-label promotion are essential to maintaining the integrity of its rigorous process for approval of drugs. The court demonstrated little sympathy for the government’s concern that pharmaceutical companies would seek to evade the new drug approval process, suggesting that the FDA could impose other requirements consistent with First Amendment principles.295 Judge Livingston, who issued a scathing dissent, retorted 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.”296 The majority opinion, if embraced by other circuits and ultimately by the U.S. Supreme Court, may substantially alter the terrain for the marketing of drug products.297

290 Defendant’s Notice of Motion and Motion in Limine to Exclude Protected First Amendment Speech or, in the Alternative, to Dismiss the Indictment; Memorandum and Points of OR, IN THE ALTERNATIVE, TO Authorities at 23, 28, United States v. Harkonen, 2009 U.S. Dist. Ct. Motions LEXIS 20231 *32, 38.

291 Id.


294 Id.

295 United States v. Caronia, 703 F.3d 149, 168-69 (2d Cir. 2012).

296 Id. at 178 (Livingston, J., dissenting). See supra Part IV.D-E (discussing Livingston’s dissent).

297 So far this has not occurred. The government declined to seek en banc review of the opinion
The government cannot and does not pursue all off-label promotion. The FDA Guidance Document sets forth a procedure for disseminating peer-reviewed reprints of the scientific literature documenting the legitimacy of off-label indications. When the government does pursue off-label promotion, it is generally to protect the integrity of the FDA approval process. One concern is that physicians cannot adequately evaluate drug claims without reviewing the label where essential information such as contraindications and drug interactions can be found. Another is the possibility that a drug company could seek approval of a product for a minimal use, even as an orphan drug subject to fast-track approval and thereafter promote it to a broader market.

The initial prediction by commentators was that Caronia would dramatically influence the government’s strategic approach toward enforcing the proscription against off-label marketing. To date, however, there is little evidence that Caronia has had the predicted impact and the government reportedly does not anticipate that it “will significantly affect the [FDA]’s enforcement of the drug misbranding provisions of the Food, Drug, and Cosmetic Act.”

or appeal to the U.S. Supreme Court. As of this date a review of the literature suggests that no lower court has followed, rejected or even considered the essential Caronia holding.

298 Gerald Masoudi, former chief counsel for the FDA told the New York Times that Caronia is “very significant . . . because it’s going to make F.D.A., in its promotion cases, focus on the kinds of speech that are more likely to harm consumers, such as false or misleading marketing versus something that is not approved.” Katie Thomas, Ruling is Victor for Drug Companies in Promoting Medicine for Other Uses, THE NEW YORK TIMES (Dec. 3, 2012), http://www.nytimes.com/2012/12/04/business/ruling-backs-drug-industry-on-off-label-marketing.html?_r=0.

299 See U.S. FDA, supra note 74.
300 See U.S. FDA, supra note 74
301 See infra note 309 and accompanying text.
302 See U.S. FDA, supra note 74.
303 21 C.F.R. pt. 316 (2013) (creating a modified approval process for "orphan" drugs). Orphan drugs treat rare diseases in order to encourage and facilitate research into drug treatments for those diseases. Id. Orphan drugs are given a modified approval process primarily because they treat rare medical conditions and companies lack the usual financial incentives to encourage the undertaking of expensive research, such as extended periods of exclusivity. Id.
the Second Circuit—and even there the court did not invalidate any portion of the FDCA. Second, the holding in Caronia is confined to cases where the government cannot prove the off-label marketing was false and/or misleading.\textsuperscript{306} Therefore, although the government relies upon the FDCA’s misbranding provisions to prosecute an array of matters constituting off-label marketing, it can still pursue those that specifically allege false and misleading promotion.\textsuperscript{307} Third, Caronia is not expected to deter prosecution of many of the off-label actions brought under the Federal False Claims Act and counterpart legislation on the books in many states.\textsuperscript{308} Such cases are often pursued by whistleblowers and require plaintiffs to establish that prescribers would not have issued prescriptions for the drugs \textit{but for} off-label promotion.\textsuperscript{309} Such cases require evidence and/or testimony that prescribers were intentionally misled by false or incomplete drug promotion by pharmaceutical marketers.\textsuperscript{310} And finally, Caronia does not prohibit the FDA from prosecuting related allegations, such as suppression of clinical studies, ghostwriting of publications, inaccurate or misleading labels or inserts, or even misrepresentation of FDA approval.\textsuperscript{311}

The government’s decision not to pursue Supreme Court review of Caronia may have been motivated by well-founded concerns about the outcome. Neither the facts nor the legal position in Caronia were particularly strong for the government. Moreover, given the Supreme Court’s holding in Sorrell that speech that facilitates pharmaceutical marketing constitutes expression protected by the First Amendment, the government may have rightly calculated that Caronia could provide an opportunity for further expansion of those safeguards that, in fact, would prove damaging to the FDA’s enforcement authority.\textsuperscript{312} In declining to appeal, the government preserves most of its enforcement tools and reserves the off-label issues for another day, preferably one when the government can prove off-label marketing that is false and/or misleading. Presumably, that day also will not be burdened with the Caronia complication that the

\textsuperscript{306} See supra Part IV (discussing Caronia).


\textsuperscript{308} See False Claims Act, 31 U.S.C. §§ 3729–33 (2009). See also supra note 110 and accompanying text (discussing cases brought under the False Claims Act).

\textsuperscript{309} False Claims Act, 31 U.S.C. §§ 3729–33 (2009). The federal False Claims Act, specifically impacts prescriptions that are funded through the Medicare or Medicaid programs because it imposes liability on contractors (individual and corporate) that fraudulently bill or collect funds from federally-funded programs. \textit{Id.}

\textsuperscript{310} \textit{Id.}

\textsuperscript{311} See supra Part IV (discussing Caronia).

\textsuperscript{312} Sorrell v. IMS Health Inc., 131 S.Ct. 2653, 2672 (2011).
off-label activity was presented as evidence of misbranding and presented as the crime in and of itself, rather than consistently framed as evidence of misbranding.\footnote{See supra note 27 and accompanying text. A drug is considered "misbranded" when it is promoted for a use not contained in the drug label (e.g., off-label). 21 U.S.C. § 355(d).}

Despite the FDA's optimism, \textit{Caronia} inevitably has influenced the agency's enforcement activities. For the moment, FDA approval is no longer the exclusive hallmark of promotional activity, and in its place, the truthfulness of the alleged claims is poised to emerge as a new standard. While the FDCA mandates rigorous double-blind, placebo-controlled clinical trials prior to promotion, that standard of proof may not prevail in an era when often unapproved drug uses have become the standard of care and, as a result, fully reimbursable by insurance companies. A company seeking to market an off-label use of its product thus might get two bites at the apple, as it can seek FDA approval for its additional use, or it can prove in a court of law that the unapproved claims are not false or misleading. If the principles of \textit{Caronia} prevail in future litigation, the requirement of clinical trial data as the standard of proof for promotional activity may no longer be sustainable under the First Amendment. In its stead, an alternative scheme for external validation, such as one that merely relies on the presence of required warnings, may emerge.

\textit{Caronia} highlights a sharp divide between those who believe pharmaceutical products should be heavily regulated (i.e., by limiting promotion to the label) and those who object to the criminalization of communications between drug companies and prescribers that are not clearly false or misleading. There is a large divide separating off-label promotion and the marketing of snake oil and it is the FDA approval that serves as gatekeeper. While the government may be concerned that the current Supreme Court might err on the side of "more speech, not less" and view off-label restrictions as "selective regulation," there is also good reason for concern about judicial rulings that fuel the marketing of the snake oil.\footnote{See United States v. Harkonen, 510 F.Appx. 633, 638-39 (9th Cir. 2013), cert. denied, 82 U.S.L.W. 3364 (U.S. Dec. 16, 2013) (No. 13-180); supra notes 13-17 and accompanying text. It was only three days after its sister circuit issued the \textit{Caronia} opinion that the Ninth Circuit heard oral argument in United States v. Harkonen. Harkonen, 510 F.Appx. at 633 (appealing to the 9th Circuit from the U.S. District Court for the Northern District of California). The basis of Harkonen's conviction was a press release announcing the alleged success of a medical study.}

\textit{Caronia} may have struck a chord that ushers in a shift in the development of FDA regulations concerning off-label promotion, but it remains to be seen whether other courts will follow the Second Circuit's lead.\footnote{Sorrell, 131 S.Ct. at 2676.}
The Caronia court acknowledged that its decision leaves the enforcement of the FDCA's misbranding provisions on shaky ground. For the moment, however, the decision's precedential value is limited and its impact sufficiently uncertain to enable the FDA to conduct business largely as usual. The outcome of Harkonen further buttresses the FDA's ability to continue regulating and pursuing blatantly false and misleading off-label promotion without regard to the potential First Amendment implications. At the same time, Caronia's impact on companies currently in various stages of investigations or negotiations with the federal government regarding alleged off-label promotion remains unclear. The "FDA is not going to roll over and play dead on this," said John Kamp of the Coalition for Healthcare Communication, predicting that the FDA will vigorously defend future cases challenging off-label regulation on First Amendment grounds. "It's too important to them it attacks the basis of most promotional regulation by FDA."