Off-Label Drug Promotion and the Use of Disclaimers

INTRODUCTION............................................................................................................. 231
I. AN OVERVIEW OF MISBRANDING AND OFF-LABEL PROMOTION........ 233
   A. The FDCA’s Misbranding Provisions and the Government’s Theory of Prosecution.......................... 233
   B. Off-Label Promotion......................................................................................... 235
II. THE CONSTITUTIONALITY OF OFF-LABEL PROMOTION
   RESTRICTIONS ................................................................................................... 238
   A. Commercial Speech Protection................................................................. 238
   B. Recent Cases: Sorrell, Caronia, and Harkonen........................................... 239
   C. Practical Effects of Recent Case Law............................................................ 244
III. A TWO-TIERED DISCLAIMER SYSTEM............................................................ 245
   A. The Current System: A Ban on Off-Label Promotion with Exceptions................................. 246
   B. The Practicability of a Disclaimer System..................................................... 246
   C. Tier One: Seeking FDA Approval................................................................. 248
   D. Tier Two: Not Seeking FDA Approval.......................................................... 249
   E. Remaining Issues......................................................................................... 250
CONCLUSION ............................................................................................................. 252

Introduction

In July 2012, the Department of Justice (DOJ) announced a record health care fraud settlement: GlaxoSmithKline would pay $3 billion, in part to resolve allegations that the company engaged in off-label promotion of pharmaceutical drugs such as Paxil and Wellbutrin. According to both the DOJ and the Food and Drug Administration (FDA), promoting a drug for an off-label use is a violation of the Federal Food, Drug, and Cosmetic Act (FDCA)’s misbranding provisions. In one of many allegations against GlaxoSmithKline, the government contended that the company unlawfully

* I would like to thank Stacy Brainin and Barry McNeil for their thoughtful guidance and suggestions throughout the writing process. I am also grateful to the staff and editors of the Texas Law Review for their hard work in editing this Note.

1. Press Release, U.S. Dep’t of Justice, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012), http://www.justice.gov/opa/pr/2012/July/12-civ-842.html. The high monetary amount was due, in part, to settlement of civil claims under the False Claims Act. Id.; see also infra note 25 and accompanying text.

2. See, e.g., Press Release, U.S. Dep’t of Justice, supra note 1 (“After the FDA approves the product as safe and effective for a specified use, a company’s promotional activities must be limited to the intended uses that FDA approved. In fact, promotion by the manufacturer for . . . ‘off-label uses’ . . . renders the product ‘misbranded.’”).
promoted Paxil for pediatric use, despite the fact that it was only approved for treating depression in individuals eighteen years of age and older.\(^3\) Other recent high-dollar settlements in off-label promotion cases include pharmaceutical company Eli Lilly’s settlement for an excess of $1.4 billion\(^4\) and Pfizer’s settlement for $2.3 billion.\(^5\)

The FDA generally prohibits marketing drugs for unapproved uses through criminal enforcement under the FDCA’s misbranding provisions.\(^6\) Although it is the government’s position that off-label promotion is illegal, the constitutionality of such a regulatory system is contested and unsettled. The Second Circuit recently held that to prevent a pharmaceutical company from promoting a lawful, albeit off-label, use of a drug violates that company’s right to free speech.\(^7\) The DOJ has resisted such an interpretation and continues to pursue claims against companies for engaging in this conduct.\(^8\) Adding more uncertainty, the Ninth Circuit recently upheld a wire fraud conviction related to off-label promotion, despite the defendant’s argument that he had a First Amendment right to circulate “a plausible scientific opinion” about an off-label use.\(^9\)

Inconsistencies surrounding the constitutionality of enforcement of the FDCA’s misbranding provisions present uncertainty for the pharmaceutical industry that is untenable.

Constitutionality aside, it remains a topic of debate whether off-label promotion should be prohibited from a policy standpoint. There is a widely acknowledged public interest in disseminating information about the medical efficacy of drugs,\(^10\) and should companies have to wait for FDA

---

3. Id.


6. See, e.g., Eli Lilly to Pay, supra note 4 (describing the criminal charge brought against Eli Lilly for introducing misbranded drugs into interstate commerce and stressing the FDA’s commitment to prosecuting off-label-marketing violations of the FDCA).


8. See infra notes 102–03 and accompanying text.


10. The FDA itself has recognized the value of this information. E.g., FOOD AND DRUG ADMINISTRATION, 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 3 (2009) [hereinafter GOOD REPRINT PRACTICES], available at http://www.fda.gov/ohrms/dockets/98fr/fda-2008-d-0053-gdl.pdf (“FDA does recognize, however, the important public health and policy justification supporting dissemination of truthful
approval before circulating this information, the resulting delay might prevent individuals from receiving possible treatments not otherwise available. But at the same time, there is a potential for abuse of off-label promotion. Critics argue that, left unregulated, pharmaceutical companies might utilize loopholes in the system, and this behavior could threaten the integrity of the current FDA-approval system and have deleterious effects on consumers of drugs for off-label uses. This Note sets forth the competing interests and proposes that the FDA implement a two-tiered disclaimer system that would allow the medical community to benefit from off-label uses while simultaneously encouraging pharmaceutical companies to secure FDA approval for these uses.

Part I examines the current regulatory scheme in place for off-label promotion and the possible benefits and consequences of allowing the promotion of off-label uses. Part II discusses how current case law regarding commercial speech threatens the government’s off-label-promotion prosecution scheme. Part III examines the current guidance-driven system and proposes a possible solution to address both the possible unconstitutionality and the policy implications of a blanket ban: The FDA could implement a two-tiered disclaimer system for off-label promotions.

I. An Overview of Misbranding and Off-Label Promotion

Despite all the agitation about off-label promotion and the monetary settlements that pharmaceutical companies have paid, nowhere in the Food, Drug, and Cosmetic Act is off-label promotion expressly prohibited. \(^{11}\) Rather, the government has read into the FDCA’s misbranding provisions a prohibition of off-label promotion.

A. The FDCA’s Misbranding Provisions and the Government’s Theory of Prosecution

The FDA must approve a drug for a specific use before that drug can be introduced into interstate commerce. \(^{12}\) The FDCA sets out requirements for FDA approval, which include clinical trials that demonstrate safety. \(^{13}\) FDA approval for a drug typically costs between $100 million and $880

---

11. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399 (2006); see also Caronia, 703 F.3d at 154 (observing that the FDCA and its implementing regulations do not expressly prohibit marketing or promoting drugs for off-label uses).
13. Id. § 355(d).
million, and the process takes anywhere from six to fifteen years to complete.14

The FDCA also prohibits the introduction of a drug into interstate commerce that is misbranded, and a drug is misbranded if, among other criteria, its label does not include “adequate directions for use.”15 The label encompasses not only the physical label on the bottle, but all the materials that accompany a drug, such as packaging inserts and advertisements.16

According to FDA regulations, the intended use of a drug “refer[s] to the objective intent of the persons legally responsible for the labeling of [the drug].”17 This intent can be determined by “oral or written statements by such persons or their representatives.”18 It is therefore the government’s contention that off-label promotion evinces an intent that the drug be used for a purpose that is not included on the label.19 Therefore, because the label does not contain adequate directions for use, the drug is misbranded in violation of the FDCA.20

Violation of the FDCA’s misbranding provisions carries criminal consequences and penalties.21 The most notable consequence is that violators of the FDCA risk being barred from participation in government health care programs.22 This penalty alone might account for pharmaceutical companies’ willingness to settle off-label promotion claims: if found criminally liable, the companies might lose lucrative business from Medicare and state health care programs. As noted by one set of

---


15. 21 U.S.C. § 331(a).

16. Id. § 352(f).

17. Id. § 321(m).


19. Id.

20. See, e.g., FOOD AND DRUG ADMINISTRATION, DRAFT GUIDANCE FOR INDUSTRY: RESPONDING TO UNSOLICITED REQUESTS FOR OFF-LABEL INFORMATION ABOUT PRESCRIPTION DRUGS AND MEDICAL DEVICES 2 (2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf (“Statements that promote a drug or medical device for uses other than those approved or cleared by FDA may be used as evidence of a new intended use.”).

21. See GOOD REPRINT PRACTICES, supra note 10, at 2–3 (“An approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include ‘adequate directions for use’ . . . .” (quoting 21 U.S.C. § 352(f))).


23. See 42 U.S.C. § 1320a-7(b)(7) (2006) (establishing the permissive exclusion from Medicare and state health care programs of entities that participate in fraud); 42 C.F.R. § 1001.901(a) (2012) (permitting the OIG to exclude entities that violate the Medicare false claims statute); id. § 1001.951(a) (permitting the OIG to exclude entities that violate the Anti-Kickback Statute).
Commentators, “[t]he Government’s business-crippling exclusion power, which may be wielded even before conviction, makes it virtually impossible to test the Government’s theories in court.”\(^\text{24}\) Additionally, FDCA violations can also be brought under the False Claims Act, which leads to monetary penalties.\(^\text{25}\)

Despite the significant penalties associated with off-label promotion for pharmaceutical companies, physicians are granted wide latitude in using their medical judgment, and are therefore allowed to prescribe drugs for off-label uses.\(^\text{26}\) In fact, depending on the field, off-label prescribing can be quite prevalent.\(^\text{27}\)

B. Off-Label Promotion

Commentators disagree about the extent to which off-label promotion should be regulated from a policy standpoint. There are numerous benefits of allowing information about alternate uses of pharmaceuticals to circulate throughout the medical community. And yet, some argue there is a potential for abuse. This subpart presents commonly articulated arguments both in favor and against permitting off-label promotion, not to assess their validity, but because these policy arguments are implicated in ensuring that a speech restriction comports with the commercial speech doctrine.\(^\text{28}\)

So why is the FDA even concerned with the off-label promotion of FDA-approved drugs? One main reason that the FDA prohibits off-label promotion is to protect the integrity of the FDA approval process. The high costs associated with FDA approval have led one set of commentators to suggest that “pharma has limited incentive to submit market-approved products for additional FDA testing. In fact, if an approved drug has a large off-label market, there is a significant financial risk for drug manufacturers


\(^{25}\) Although the penalties associated with False Claims Act violations are not the subject of this Note, it is worth mentioning that these violations result in monetary fines. For example, the settlements of GlaxoSmithKline, Eli Lilly, and Pfizer were of FCA claims brought for violations of the FDCA. See supra notes 1, 4–5 and accompanying text. For a discussion of liability for off-label promotion under the False Claims Act, see generally Stephanie Greene, False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products, 110 PENN ST. L. REV. 41 (2005).


\(^{27}\) See Randall S. Stafford, Regulating Off-Label Drug Use—Rethinking the Role of the FDA, 358 NEW ENG. J. MED. 1427, 1427 (2008) (noting that a 2006 study of 160 common drugs indicated that off-label uses accounted for 21% of prescriptions).

\(^{28}\) See infra notes 45–51, 81–84, and accompanying text.
in seeking FDA validation for these uses.”

Another commentator notes, “[t]he FDA was concerned that manufacturers would get approval for a ‘cheap, narrow indication and the next day begin selling the drug for multiple, broad, and profitable other indications.” Ultimately, a ban on off-label promotion addresses concerns that a company might “circumvent existing regulatory protections.”

Without FDA approval, the medical community might not be sure of the safety and efficacy of an off-label use. Pharmaceutical companies conduct their own research into off-label uses, but there is debate as to the reliability of such studies. In their article on off-label promotion, Dr. Fazal Khan and Justin Holloway discuss the practice of “ghostwriting,” whereby a pharmaceutical company hires organizations to distribute articles about off-label uses of drugs, but the affiliation between the article and the company is not made known to the public. “Because physicians rely on medical literature,” one commentator notes, “the concern about ghostwriting is that doctors might change their prescribing habits after reading certain articles, unaware they were commissioned by a drug company.”

Khan and Holloway’s article also discusses the use of gag clauses to prevent unfavorable results from company-sponsored studies from reaching the public. Clinical trial agreements between pharmaceutical companies and private research organizations might contain clauses that prevent third parties from examining the data from trials. Khan and Holloway argue that the ultimate effect of gag clauses is that “[n]egative results are . . . routinely underreported or unreported altogether.”

Practices such as ghostwriting and using gag clauses could result in a lack of data transparency that leaves the medical community in the dark as

31. Id. at 206.
32. See generally Christopher T. Robertson, The Money Blind: How to Stop Industry Bias in Biomedical Science, Without Violating the First Amendment, 37 AM. J.L. & MED. 358 (2011) (arguing that there is inherent bias in scientific research that is paid for by pharmaceutical companies).
33. See Khan & Holloway, supra note 29, at 418–20 (describing the logistics of ghostwriting).
36. Id. at 421.
37. Id.
to the medical benefits and risks of off-label uses. This lack of information could have detrimental effects when a drug becomes widely prescribed for an off-label use.38

Yet despite these apparent risks, there are noted benefits of off-label promotion. The most obvious is that the public health is improved where physicians are made aware of alternative treatment programs and can knowledgeably prescribe medicine for these uses.39 During general clinical trials, a pharmaceutical company might become aware of a new potential use for a drug. Because of the time and cost associated with approving drugs for new uses, if such approval were required for marketing, the company might make a conscious decision to forgo approval and not discuss this off-label use with the medical community.40 In such a situation, the public would lose access to a potential treatment for an ailment.41

The high cost of FDA approval underlies several other justifications for allowing off-label promotion. It could be argued that allowing marketing for off-label uses decreases the costs of drugs to the consumers. Should pharmaceutical companies be required to seek approval for all uses, any increased cost associated with FDA approval might be passed on to the public through price increases.42 Additionally, requiring costly FDA approval might stifle innovation in pharmaceutical companies, which is contrary to the public health goal of wide access to treatment.

Considering all of these factors, it remains a topic of debate whether off-label promotion is an area that warrants such a strict regulatory scheme.


39. See Coleen Klasmeier & Martin H. Redish, Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection, 37 AM. J.L. & MED. 315, 318 (2011) (“[B]oth patients and prescribers would often be aided by the dissemination of information to the medical profession about these valuable off-label uses—uses that health care practitioners may well be unfamiliar with absent such communications.”); see also Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 56 (1998) (“As off-label uses are presently an accepted aspect of a physician’s prescribing regimen, the open dissemination of scientific and medical information regarding these treatments is of great import.”). The FDA has there is an “important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications” about off-label uses. GOOD REPRINT PRACTICES, supra note 10.

40. See Salbu, supra note 30, at 193–94 (“Proponents of off-label processes focus predominantly on their potential to expedite the development and availability of effective new treatments. . . . If off-label use of drugs can help patients, then off-label marketing may enable the greatest number of potential beneficiaries to receive the treatments best suited to their needs.”).

41. This is frequently the case with “orphan” diseases—diseases so rare that seeking FDA approval for a drug use is not justifiable for the pharmaceutical company from a cost standpoint. Gregory Conko, Hidden Truth: The Perils and Protection of Off-Label Drug and Medical Device Promotion, 21 HEALTH MATRIX 149, 155–56 (2011).

42. Salbu, supra note 30, at 195.
II. The Constitutionality of Off-Label Promotion Restrictions

Regardless of whether off-label promotion should be regulated from a public policy perspective, the constitutionality of a blanket ban on such promotion is a widely contested and discussed issue, especially in the wake of recent litigation. Opponents of the current ban on off-label promotion argue that a ban on truthful, nonmisleading speech is a violation of the First Amendment’s free speech protection.\(^{43}\) Advocates of the current system respond that the government has an interest in regulating such speech.\(^{44}\)

A. Commercial Speech Protection

In *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*,\(^{45}\) the Supreme Court set forth the commercial speech test.\(^{46}\) Under this four-part test, a government restriction on speech is permissible where (1) it concerns lawful, nonmisleading speech, (2) the government has a substantial interest in regulating the speech, (3) the regulation directly advances this substantial interest, and (4) the restriction is not more extensive than necessary to achieve the substantial interest.\(^{47}\)

In 2002, the Court heard a challenge to restrictions on drug advertisement in *Thompson v. Western States Medical Center*.\(^{48}\) In determining that a ban on a physician’s compound-drug advertisement was unconstitutional, the Court found that the restriction was not narrowly tailored so as to satisfy the fourth prong of the test.\(^{49}\) Although acknowledging that the government had a substantial interest in, *inter alia*, “preserv[ing] the effectiveness and integrity of the FDCA’s new drug approval process and the protection of the public health that it provides,”\(^{50}\) the Court noted alternatives available to achieve this interest in a more tailored way.\(^{51}\)

43. E.g., Klasmeier & Redish, *supra* note 39, at 349 (“[T]he FDA’s prohibition of manufacturer’s off-label promotion of prescription drugs unambiguously violates the controlling doctrinal framework for the constitutional protection of commercial speech.”).

44. E.g., Margaret Gilhooley, *Commercial Speech, Drugs, Promotion and a Tailored Advertisement Moratorium*, 21 HEALTH MATRIX 97, 97 (2011) (noting that “the safety risks to the public rightly deserve great weight under the commercial speech doctrine”). *See generally, e.g.*, David Orentlicher, *The Commercial Speech Doctrine in Health Regulation: The Clash Between the Public Interest in a Robust First Amendment and the Public Interest in Effective Protection from Harm*, 37 AM. J.L. & MED. 299 (2011) (weighing the First Amendment and public health interests in discussing off-label promotion).

45. 447 U.S. 557 (1980).

46. *Id.* at 566.

47. *Id.*


49. *Id.* at 371–72.

50. *Id.* at 368 (alteration in original) (internal quotation marks omitted).

51. *Id.* at 372.
Given the similarities between drug advertisement in *Western States Medical* and off-label drug promotion under the FDCA, this decision sparked commentators to predict the impending demise of the off-label promotion ban. Immediately following *Western States Medical*, the FDA solicited comments from the public in an effort to determine the constitutionality of a variety of the FDCA’s statutory provisions. The notice asked, among other questions, “[w]ould permitting speech by manufacturer, distributor, and marketer about off-label uses undermine the [FDCA]’s requirement that new uses must be approved by the FDA? If so, how? If not, why not? What is the extent of FDA’s ability to regulate speech concerning off-label uses?” Many of the comments the FDA received in response to its request maintained that the off-label promotion ban was unconstitutional. Pfizer’s response, for example, urged the FDA to “refine its existing guidelines to broaden and clarify permitted non-promotional dissemination of off-label information.”

**B. Recent Cases: Sorrell, Caronia, and Harkonen**

Yet despite the flurry of concern, over a decade later, the Supreme Court has yet to rule on the constitutionality of a general ban on off-label promotion. Recent cases have signaled not only some distaste for the somewhat permissive commercial speech test, but also that a challenge to the constitutionality of an off-label promotion ban in the Supreme Court might be successful.

In 2011, the Court heard a First Amendment challenge to a Vermont statute that restricted “data-mining,” in *Sorrell v. IMS Health Inc*. The law at issue generally prohibited the sale of pharmacy records regarding physician-prescribing practices for the purposes of marketing. Noting that

---

52. See, e.g., A. Elizabeth Blackwell & James M. Beck, *Drug Manufacturers’ First Amendment Right to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory*, 58 FOOD & DRUG L.J. 439, 439 (2003) (“The constitutionality of [off-label promotion] policies has long been questioned, and the Supreme Court’s recent decision in *Thompson v. Western States Medical Center* raises to new heights doubts regarding FDA’s ability to withstand First Amendment challenge in this area.” (footnote omitted)); Jeffrey N. Gibbs et al., *Ripe for Revision: Reassessing the Constitutionality of Food and Drug Administration Restrictions on Protected Speech*, 58 FOOD & DRUG L.J. 331, 332 (2003) (“FDA’s policies that restrict the dissemination of truthful scientific information that may discuss off-label uses of approved products are vulnerable to attack on constitutional grounds.”).


54. *Id.* at 34,944.


57. 131 S. Ct. 2653 (2011).

58. *Id.* at 2659.
the statute was content based and speaker based, the Court determined the statute was subject to heightened judicial scrutiny.\(^59\) The court also commented that concluding that the restrictions were content based was “all but dispositive.”\(^60\) In striking down the restriction as unconstitutional, the Court noted that the restriction did not advance the government’s interest in preserving the privacy of physicians because the information could be sold for any purpose besides marketing.\(^61\) Much like the response to \textit{Western States Medical}, because of the similarities between the data-mining restriction in \textit{Sorrell} and off-label promotion restrictions, commentators noted that \textit{Sorrell} might signal the end of the off-label promotion ban.\(^62\)

By far the most notable off-label promotion case to date is the Second Circuit’s recent decision in \textit{United States v. Caronia}.\(^63\) “[T]he decision in \textit{United States v. Caronia},” according to one source, “has the potential to turn the criminal enforcement scheme of the Federal Food, Drug and Cosmetic Act, or FDCA, on its head.”\(^64\) At trial, Alfred Caronia, a pharmaceutical representative for Orphan Medical, Incorporated, was found guilty of conspiracy to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. § 331(a).\(^65\) The drug at issue, Xyrem, is a central-nervous-system depressant that is approved by the FDA for narcoleptics with cataplexy or excessive daytime sleepiness.\(^66\) Xyrem must be accompanied by a “black box” warning notifying consumers “that the drug’s safety and efficacy were not established in patients under 16 years of age, and the drug had ‘very limited’ experience among elderly patients.”\(^67\)

Despite these approved uses, Caronia was recorded suggesting to a prospective customer that the drug could be used for insomnia, fibromyalgia, periodic leg movement, Parkinson’s, other sleep disorders, muscle disorders, chronic pain, and daytime fatigue.\(^68\) On other occasions, Caronia and Dr. Peter Gleason, a doctor hired by Caronia to discuss Xyrem at “speaker programs,” were recorded suggesting the drug could be used in

---

\(^{59}\) \textit{Id.} at 2663–64.

\(^{60}\) \textit{Id.} at 2667.

\(^{61}\) \textit{Id.} at 2668.

\(^{62}\) \textit{See, e.g.,} Lynn C. Tyler, \textit{The FDA’s Regulation of Off-Label Promotion: Has the Supreme Court’s Opinion in \textit{Sorrell} v. IMS Health Cracked the Foundation?}, in \textit{RECENT DEVELOPMENTS IN FOOD AND DRUG LAW} 41, 42 (2013 ed.) (“[A]t a minimum, [\textit{Sorrell}] casts some doubt on the constitutionality of the FDA’s regulation of off-label promotion.”).

\(^{63}\) 703 F.3d 149 (2d Cir. 2012).


\(^{65}\) \textit{Caronia}, 703 F.3d at 152, 155–56.

\(^{66}\) \textit{Id.} at 155.

\(^{67}\) \textit{Id.}

\(^{68}\) \textit{Id.} at 156.
children under the age of sixteen and in adults older than sixty-five.69 Caronia moved to dismiss the charges on the basis that an application of the FDCA’s misbranding provisions to prohibit his conduct was unconstitutional under the First Amendment.70 The trial court denied the motion, and Caronia was found guilty of conspiracy to misbrand at trial in October 2008.71

On appeal, the Second Circuit relied heavily upon the Court’s decision in Sorrell.72 In fact, because Sorrell was decided while this case was pending on appeal, the Second Circuit ordered supplemental briefing regarding what impact, if any, the Supreme Court’s decision in Sorrell had upon Caronia.73 The majority opinion used Sorrell to decide that the government’s construction of the FDCA’s misbranding provisions constituted content-based and speaker-based restrictions on speech.74 A ban on off-label promotion, the court determined, is content based because “it distinguishes between favored speech and disfavored speech on the basis of the ideas or views expressed.”75 The off-label restrictions permit speech about FDA-approved uses but prohibit speech about off-label use, despite the off-label use itself being permissible.76 And the restriction is speaker based because, while pharmaceutical companies are prohibited from discussing off-label uses, academics and individuals in the medical community are free to discuss and prescribe for these uses.77

Having determined the restrictions qualified for heightened judicial scrutiny, the court then determined the government’s application of the misbranding provisions could not withstand even the less stringent standard under Central Hudson.78 The speech was not false or misleading under prong one because it concerned off-label use, which was lawful and because off-label promotion “is not in and of itself false or misleading.”79 In examining the second prong, the court agreed with the government that there existed a substantial governmental interest in “preserving the effectiveness and integrity of the FDCA’s drug approval process, and . . . reducing patient exposure to unsafe and ineffective drugs.”80

69. Id. at 156–57.
70. Id. at 158.
71. Id. at 158–59.
72. Id. at 163.
74. Caronia, 703 F.3d at 164.
75. Id. at 165 (internal quotation marks omitted).
76. Id.
77. Id.
78. Id. at 164–68.
79. Id. at 165.
80. Id. at 166. See supra subpart I(B) for a discussion of these policy arguments.
The court determined that the restriction on off-label promotion did not satisfy the third or fourth prongs of the test and, in doing so, invoked many of the policy considerations discussed previously in subpart I(B). When examining whether the restriction advanced the government’s interest, the court focused on the legality of off-label use and noted that the restriction “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.”

The restriction also failed the fourth prong of the test, as the court determined it was more extensive than necessary. The court noted many alternatives available to the government that would achieve its interest in a more tailored way. Because the off-label promotion restriction could not pass the Central Hudson test, the court determined that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug.”

Despite the semblance of clarity that the majority opinion in Caronia offers, the ban on off-label promotion is not dead. The FDA declined to file a writ of certiorari, stating that the agency “does not believe that the [Caronia] decision will significantly affect the agency’s enforcement of the drug misbranding provisions of the [FDCA].” One commentator notes that this decision might be tactical: The FDA might be concerned that Caronia would give the Court an opportunity to expand Sorrell by striking down the FDA’s current prosecution scheme, and it would rather wait for a case involving particularly egregious conduct on the part of the defendant to test its prosecution theories. If the Supreme Court struck down a ban on off-label promotion, it would surely be, as noted in the dissent in Caronia, the end of “the very foundations of our century-old system of drug regulation.”

81. Caronia, 703 F.3d at 166 (emphasis added) (internal quotation marks omitted).
82. Id. at 167.
83. Id. at 167–68.
84. Id. at 169.
86. See Ellyn L. Sternfield, FDA Will Not Appeal Second Circuit Decision in U.S. v. Caronia, JD SUPRA L. NEWS, Jan. 30, 2013, http://www.jdsupra.com/legalnews/fda-will-not-appeal-second-circuit-decis-61328/ (“By not appealing Caronia, the FDA preserves the enforcement authority left intact by Caronia and its First Amendment arguments for a FDCA case in which it has a stronger position, such as when the marketing at issue is alleged to be false or misleading.”).
87. Caronia, 703 F.3d at 169 (Livingston, J., dissenting).
Adding another level of complexity is the Ninth Circuit’s recent decision in United States v. Harkonen, in which the court upheld the wire fraud conviction of the former Chief Executive Officer of InterMune Incorporated. Although Harkonen was initially indicted for both misbranding and wire fraud, a jury found him guilty only of wire fraud. The wire fraud conviction was based on a press release that circulated information about an off-label use of the drug Actimmune. The drug was approved for the treatment of two rare pediatric diseases, and InterMune conducted a clinical trial to determine if the drug would be effective for another use: to treat idiopathic pulmonary fibrosis. Harkonen issued a press release discussing the success of this trial, yet the Ninth Circuit maintained that “[a]t trial, nearly everybody actually involved in [the clinical trial] testified that the Press Release misrepresented [the] results.” In a brief opinion, the Ninth Circuit upheld the conviction and found unpersuasive the defendant’s argument that the conviction violated his First Amendment rights, stating that “[t]he First Amendment does not protect fraudulent speech.”

Because of the connection with off-label promotion, Harkonen has been closely followed by the medical community, and many might be confused about how the courts’ decisions in Harkonen and Caronia might be reconciled. The most obvious difference between these cases is the perceived nature of the speech at issue. Albeit brief, the Ninth Circuit’s opinion spoke quite unfavorably about what it saw as the fraudulent nature of the press release’s contents, whereas the Second Circuit noted that

88. 510 F. App’x 633 (9th Cir. 2013).
91. See Brief for the United States as Appellee/Cross-Appellant at 23–27, Harkonen, 510 F. App’x 633 (Nos. 11-10209 & 11-10242) (discussing the contents of the press release at issue and framing the press release as the basis of Harkonen’s wire fraud conviction).
92. Id. at 5–7.
93. Harkonen, 510 F. App’x at 636. The court noted that, in analyzing the data, Harkonen stated that he would “cut that data and slice it until [he] got the kind of results [he was] looking for.” Id. (alterations in original) (internal quotation marks omitted).
94. Id.
95. See, e.g., Chan & Klaber, supra note 64, at 1 (“Though Harkonen was not convicted under the FDCA . . . his appeal still stands to have a significant effect on determining what pharmaceutical companies and their sales representatives can and cannot say in promoting drugs.”).
Caronia’s speech was truthful and nonmisleading. Additionally, in *Harkonen*, the court did not even apply the commercial speech test.

On March 29, 2013, Harkonen filed a petition for rehearing en banc, which was denied on May 7, 2013. On August 5, 2013, Harkonen filed a petition for a writ of certiorari: any subsequent decision might clarify any possible tension between these two cases.

C. Practical Effects of Recent Case Law

After the Second and Ninth Circuits’ respective opinions in *Caronia* and *Harkonen*, there remains confusion over the constitutionality of the current enforcement scheme of the FDCA’s misbranding provisions. One commentator has predicted a shift in government rhetoric following *Caronia*: whereas previous announcements of settlements contained allegations of “off-label promotion,” a recent DOJ press release instead focused on the company’s intent that a drug be used for off-label purposes. A shift in the focus back onto the misbranding provisions themselves perhaps evinces the FDA’s unwillingness to renounce its position on off-label promotion. This is also supported by the FDA’s statement that “it does not believe that the *Caronia* decision will significantly affect the agency’s enforcement of the drug misbranding provisions of the Food, Drug, and Cosmetic Act.”

Although some companies have filed for injunctive relief from prosecution under the FDCA’s misbranding provisions on First Amendment grounds, those cases have settled before the First Amendment issue was heard. For example, Allergan, Incorporated, filed for a declaratory...
judgment in the United States District Court for the District of Columbia. In its memorandum in support, the company argued, inter alia, that “Allergan’s [off-label promotion speech] is protected as ‘commercial speech’ under the Supreme Court’s recent decision in Western States.” The following year, Allergan reached a settlement with the government wherein it agreed to plead guilty to misbranding and to pay $600 million. As part of the settlement, the company agreed to dismiss the First Amendment action against the government. A similar arrangement was recently made with Par Pharmaceutical, wherein the company agreed to dismiss injunctive relief claims as part of a larger agreement to resolve allegations that it promoted the drug Megace ES for off-label uses. Therefore, even though the constitutionality of a ban on off-label promotion has been brought into question, courts have been unable to reach the constitutional issue in these declaratory-judgment actions.

III. A Two-Tiered Disclaimer System

To address the concerns expressed by both the Second Circuit in Caronia and critics of the current regulatory scheme, the FDA must address prong three and prong four of the Central Hudson test.

Faced with the possible unconstitutionality of the current system, the FDA needs to balance the competing arguments in favor and against allowing off-label promotion. It must create a system that allows the benefits of off-label promotion, specifically the dissemination of information regarding alternative treatment options, while addressing any potential negatives by encouraging companies to seek FDA approval for new uses and to explain the science behind the claims of efficacy. A two-tiered disclosure system could accomplish these goals.

105. Id. at 21.
107. Id.
109. Commentators have offered several potential solutions to align off-label promotion regulations with the First Amendment. See, e.g., Blackwell & Beck, supra note 52, at 459–61 (discussing various nonspeech-restrictive approaches the FDA could take to regulate off-label promotion).
A. The Current System: A Ban on Off-Label Promotion with Exceptions

The current off-label promotion ban does contain some exceptions, which take the form of nonbinding recommendations that are set forth in FDA guidance publications.\textsuperscript{110} Most notably, the FDA permits pharmaceutical companies to reprint medical journal articles that discuss unapproved new uses, subject to certain requirements.\textsuperscript{111} Under the guidance, if a pharmaceutical company complies with the requirements, the FDA “does not intend to consider the distribution of such medical and scientific information . . . as establishing intent that the product be used for an unapproved new use.”\textsuperscript{112} Under a draft guidance released in December 2011, pharmaceutical companies would be able to respond to unsolicited requests about off-label uses.\textsuperscript{113}

But, for the most part, these guidances do not cover the type of broad activity at issue in cases like \textit{Caronia}. Where pharmaceutical representatives discuss unapproved uses with the medical community, these casual conversations are unlikely to involve unsolicited requests for information or distribution of reprinted journal articles. Therefore, the FDA could implement guidance that covers this type of activity; this could be accomplished with the creation of a disclaimer system that requires pharmaceutical companies and their representatives to disclose certain information when discussing off-label uses of a drug.

B. The Practicability of a Disclaimer System

There are four main benefits to the use of a disclaimer system to regulate off-label promotion.

First, creating a disclaimer system recognizes the general constitutionality of the FDCA’s misbranding provisions. \textit{Caronia} did not strike down these provisions, just the enforcement system that criminalized truthful, nonmisleading speech.\textsuperscript{114} There is no need, therefore, to overhaul the entire system. Rather, a disclaimer system can be created in the same

\textsuperscript{110} See 21 C.F.R. § 10.115(b)(1) (2012) (“Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue.”).

\textsuperscript{111} See \textit{GOOD REPRINT PRACTICES}, supra note 10, at 3 (acknowledging, implicitly, that distribution of truthful and nonmisleading publications to health care professionals may advance public health and setting forth criteria for both the substance of medical journal articles and the means of disseminating such articles).

\textsuperscript{112} \textit{Id.} at 4.

\textsuperscript{113} See \textit{FOOD AND DRUG ADMINISTRATION}, supra note 20, at 6 (recognizing that the FDA has “long taken the position” that pharmaceutical companies can respond to such unsolicited requests so long as they “provid[e] truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to a specific request” and that this is so even if the response consists of “unapproved or uncleared indications or conditions of use”).

\textsuperscript{114} United States v. Caronia, 703 F.3d 149, 168–69 (2d Cir. 2012).
way that the FDA has created the exceptions for reprint circulations and responses to unsolicited requests. The FDA can create a “Guidance for Industry” that announces that the FDA has no intention of bringing misbranding charges against individuals and entities that discuss off-label uses in accordance with the contents of the guidance.

Second, the FDA’s requirement of disclaimers in other areas makes the use of disclaimers for off-label promotion feasible from an administrability standpoint. Disclaimers are familiar to pharmaceutical companies. Anybody who watches television has seen countless advertisements for drugs that contain a lengthy recitation of potential side effects. This is because the FDA requires that drug advertisements include a “[t]rue statement of information in brief summary relating to side effects, contraindications, and effectiveness.” Such mandated statements are commonplace in the industry, and this familiarity makes it possible for the FDA to require disclosure of certain information when promoting a drug for an off-label use.

Third, a disclaimer system can be tailored in a way to address the government’s concerns with off-label promotion while simultaneously encouraging the benefits of promotion and would, therefore, satisfy the third prong of the Central Hudson test. The government can materially advance its stated interest in protecting the FDA-approval process and consumer safety by creating a two-tiered disclaimer system. The government can create one set of disclaimers for the discussion of off-label uses of drugs for which the company is seeking FDA approval, and a second, more rigorous set of disclaimers that would apply if the company were not seeking FDA approval for the off-label use. The system would therefore encourage companies to seek FDA approval of new uses while increasing the public’s access to information on medical alternatives.

Finally, the use of disclaimers has been widely acknowledged by courts as a constitutional alternative to an outright ban on speech and thus would satisfy the fourth prong of the Central Hudson test. In Caronia, in determining that a blanket ban on off-label promotion failed to meet the fourth prong, the Second Circuit noted several alternatives available to the government that would advance its interests. Among the alternatives was the use of disclaimers: “The government could develop its warning or disclaimer systems . . . .” Disclaimers were mentioned as a constitutional alternative to commercial speech restrictions in Western States Medical.

115. See supra notes 110–13 and accompanying text.
117. Caronia, 703 F.3d at 168.
118. Id.
Citizens United v. Federal Election Commission, Pearson v. Shalala, and Washington Legal Foundation v. Friedman. As stated by the district judge in Washington Legal Foundation, requiring disclaimers “comports with the Supreme Court’s preference for combating potentially problematic speech with more speech.” Should the FDA implement such a system, it would therefore likely placate critics of the current system by addressing concerns that the restriction is too broad. The following subpart provides an example of what a two-tiered disclaimer system could look like in practice, although the individual disclaimer requirements within each tier could be altered as needed to increase the system’s effectiveness.

C. Tier One: Seeking FDA Approval

The first tier would apply to the promotion of a drug for an off-label use for which the pharmaceutical company is currently seeking FDA approval and would require disclaimers that address the government’s concern with the lack of data transparency and the possible detrimental effects that off-label uses could have on the public. In this tier, off-label promotion of a drug should include disclosure of possible side effects associated with consumption of the drug. The disclaimer should include a statement that the off-label use is not approved by the FDA and an acknowledgment that the purpose of the FDA is to ensure that drugs introduced into the marketplace are safe and effective. The FDA could require the pharmaceutical company to disclose, where applicable, that studies have not yet reached the level of statistical significance required for FDA approval.

120. 558 U.S. 310, 368 (2010).
121. 164 F.3d 650, 655–60 (D.C. Cir. 1999).
123. Id.; see also Whitney v. California, 274 U.S. 357, 377 (1927) (Brandeis, J., concurring) (“[T]he remedy to be applied is more speech, not enforced silence.”).
124. For a pre-Caronia discussion of the use of disclaimers for circulating reprints, see Margaret Gilhooley, Drug Regulation and the Constitution After Western States, 37 U. RICH. L. REV. 901, 921–30 (2003). See also Kristie LaSalle, A Prescription for Change: Citizens United’s Implications for Regulation of Off-Label Promotion of Prescription Pharmaceuticals, 19 J.L. & POL’Y 867, 907–10 (2011) (noting how the Court’s discussion of disclaimers in Citizens United signals the applicability of disclaimers to off-label promotion regulation). The FDA’s guidance for reprint practices also contains requirements that reprints “be accompanied by a prominently displayed and permanently affixed statement disclosing” various information. GOOD REPRINT PRACTICES, supra note 10, at 5–6.
125. A similar disclosure is required for circulating reprints. GOOD REPRINT PRACTICES, supra note 10, at 5–6.
126. This statement is also required when circulating reprints. Id.
127. Professor Gilhooley recommended such a disclaimer for reprints, noting that “the physician needs the benefit of knowing how the studies in the medical journal differ from the testing the FDA requires.” Gilhooley, supra note 124, at 927. Therefore, she recommended that “[t]o adequately inform physicians, there should be a disclosure reporting the extent to which the
All of these statements are truthful, nonmisleading statements about the testing and FDA approval of the drug and serve the purpose of informing the physicians and the medical community that the efficacy of this substance has not yet been established within FDA standards. Of course, once the FDA-approval process is complete for the off-label use, this disclaimer would no longer be necessary in promoting the drug for that approved use.

D. Tier Two: Not Seeking FDA Approval

The second tier of the disclaimer system would apply to the discussion of an off-label use for which the pharmaceutical company is not seeking FDA approval. This tier should therefore contain heightened requirements aimed at encouraging the company to seek FDA approval so that less stringent disclaimers apply to the promotion.

In addition to the statements required in the first tier, when promoting a drug for an off-label use for which the company is not seeking FDA approval the pharmaceutical company should disclose the relationship between the organization that conducted any studies and the manufacturer so as to decrease any appearance of impartiality.128

The FDA could also require the pharmaceutical company to state, where applicable, that depending on the method of analysis, the underlying data might not support the stated conclusions and that the scientific community might not agree on the conclusiveness of the study.129 Tier-two disclaimers should also include an acknowledgment that proving the efficacy and safety of drugs for this use requires continuous and ongoing testing.

Finally, the company might be required to disclose all testing that reached conclusions that are inconsistent with the claims of efficacy or safety contained in the off-label promotion.130 The government could
therefore ensure that the medical community is making informed prescribing decisions based on the entirety of the data available.

These additional requirements are not so onerous that the company will forgo off-label promotion altogether, but are enough of a burden that the company might seek FDA approval to reach a lower standard of disclaimers. Under a two-tiered system, pharmaceutical companies are encouraged to seek FDA approval for off-label uses, and this achieves the government interest in protecting the FDA-approval process. The disclaimer system also requires the company to disclose information that would increase data transparency.

Therefore, the system satisfies the third prong of the Central Hudson test: a two-tiered disclaimer system materially advances the government’s interest in “preserving the effectiveness and integrity of the FDA’s drug approval process, and . . . reducing patient exposure to unsafe and ineffective drugs.”

E. Remaining Issues

Despite the benefits of this system, the issue remains whether the FDA would require agency approval of disclaimers prior to off-label promotion. For comparison purposes, the FDA does not require approval of most drug advertisements prior to publication. From an administrability standpoint, the FDA might not be able to review all off-label drug disclaimers quickly, and any delay in securing required approval would frustrate the main benefit of off-label promotion: having scientific information available to the medical community. Additionally, any disclaimer guidance issued would reflect an enforcement scheme that the FDA will not prosecute those that comply with the disclaimer requirements. There would be, therefore, an initial agency determination of whether disclaimers do comport with the recommendations prior to prosecution for misbranding.

A second issue concerns whether the proposed system sufficiently encourages companies to seek FDA approval for new uses. Some commentators have expressed skepticism that “simple” disclaimers might

---

131. United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012).
132. When discussing the use of disclaimers for reprint distribution, Professor Gilhooley advocated for a notification requirement whereby the manufacturer submitted materials to the FDA. Gilhooley, supra note 124, at 928–29. Professor Gilhooley noted that in Pearson v. Shalala, the D.C. Circuit recognized the need for FDA approval of disclaimers in the context of unapproved claims on dietary supplements. Id. at 929 (citing Pearson v. Shalala, 164 F.3d 650, 657–58 (D.C. Cir. 1999)).
133. Carver, supra note 55, at 164.
134. See supra subpart III(A).
not achieve this government interest.\textsuperscript{135} While a two-tiered system might address concerns with a “simple” disclaimer system, the FDA could combine this disclaimer system with additional programs targeted to incentivize companies to seek FDA approval. For example, the FDA might also require that companies seek FDA approval for new uses once prescriptions for those uses reach a specified threshold, or the FDA could “create new benefits that accrue upon receipt of new drug approval.”\textsuperscript{136} The FDA is not required to implement a single policy to advance all of its interests. As noted by the court in \textit{Caronia} when discussing possible alternative restrictions, “[t]he possibilities are numerous indeed.”\textsuperscript{137}

A final issue is whether a two-tiered disclaimer system would withstand “heightened judicial scrutiny,” assuming such a standard applies to off-label speech restrictions. In \textit{Caronia}, the Second Circuit determined that, under \textit{Sorrell}, heightened scrutiny does apply,\textsuperscript{138} yet the court examined the restriction using the “intermediate” standard under \textit{Central Hudson}.

One set of commentators has suggested that “[i]t is possible that \textit{Sorrell} failed to articulate a specific standard of review.”\textsuperscript{140} The precise manner in which speech restrictions for off-label marketing would be examined under heightened judicial scrutiny is therefore uncertain. Future application of heightened judicial scrutiny to would-be commercial speech restrictions by courts in other contexts will help clarify this important issue.

\textsuperscript{135} See Conko, \textit{supra} note 41, at 180 (“[S]imple disclaimers alone may not be sufficient to incentivize manufacturers to navigate the supplemental approval process.”); \textit{see also} Blackwell & Beck, \textit{supra} note 52, at 457 (“R}eplacing FDA’s existing speech-restrictive policies with narrower speech restrictions, while it might advance FDA’s interest in preventing consumer deception, would leave FDA still in search of new policies designed to advance its interest in maintaining control over ‘new’ uses of regulated products.”).

\textsuperscript{136} Blackwell & Beck, \textit{supra} note 52, at 459–61 (describing potential nonspeech-restrictive alternatives to regulating off-label promotion that would encourage a company to seek FDA approval for new uses).

\textsuperscript{137} United States v. Caronia, 703 F.3d 149, 168 (2d Cir. 2012).

\textsuperscript{138} \textit{See supra} notes 72–77 and accompanying text.

\textsuperscript{139} \textit{See supra} note 78 and accompanying text.

\textsuperscript{140} Marc J. Scheineson & Guillermo Cuevas, \textit{United States v. Caronia: The Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion As “False and Misleading,”} 68 \textit{FOOD & DRUG L.J.} 201, 210 (2013); \textit{see also} Tamara R. Piety, “A Necessary Cost of Freedom”? \textit{The Incoherence of Sorrell v. IMS,} 64 \textit{ALA. L. REV.} 1, 53–54 (2012) (stating that the Court in \textit{Sorrell} did not “explicitly overruled” \textit{Central Hudson} or acknowledged that it was announcing a new standard by which to evaluate commercial speech” and that “the Court rendered the commercial speech doctrine incoherent and sowed further confusion about what the appropriate test is”).
Conclusion

Off-label promotion has its benefits: it allows scientific information about potential treatments to be circulated in the medical community and increases the public’s access to these treatments. Currently, the FDA sees the potential for abuse of off-label promotion as too great and has created a restriction on off-label promotion that recent case law indicates might be struck down as unconstitutional at any moment.

A two-tiered disclaimer system is a potential solution to this problem. By requiring all off-label promotions to be accompanied by information about the science behind the claims, the FDA increases data transparency. And by increasing the disclaimer burden for promotion of drugs for which the manufacturer is not seeking FDA approval, the FDA encourages manufacturers to seek FDA approval. Not only does this system advance the government’s interest, it is so narrowly tailored as to withstand constitutional analysis under the *Central Hudson* test.

—Dina McKenney