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Side Effects May Vary: The Aftermath of the United States v. Caronia Decision on Off-Label Drug Promotion

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By Christina Le

Christina.Le1@student.shu.edu

Introduction

On November 4, 2013, health care giant Johnson & Johnson agreed to pay more than $2.2 billion to resolve criminal and civil allegations of off-label marketing of three of its prescription drugs: Risperdal, Invega, and Natrecor.[1] The civil settlement with federal and several state governments totaled $1.72 billion.[2] Further, criminal fines and forfeitures reached $485 million. This settlement was the second largest health care fraud settlement in United States history.[3] Less than four months later, Endo Health Solutions, Inc. and its subsidiary, Endo Pharmaceuticals, Inc., agreed to pay $192.7 million to resolve criminal and civil claims for the off-label promotion of the drug, Lidoderm.[4] In a statement about the settlement, Zane D. Memeger, United States Attorney for the Eastern District of Pennsylvania, stated, "pharmaceutical companies have a legal obligation to promote their drugs for only FDA-approved uses."[5] But what about their constitutional right to free speech? The United States

[1] Office of Public Affairs, Department of Justice, "Johnson & Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations" (2013) (available at: http://www.justice.gov/opa/pr/2013/November/13-ag-1170.html).
[2] *Id*.
[3] The largest health care fraud settlement involved GlaxoSmithKline when it pled guilty and agreed to pay $3 billion to resolve claims of unlawfully promoting prescription drugs, failing to report safety data, and allegedly engaging in false price reporting practices. Office of Public Affairs, Department of Justice, "GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data" (2012) (available at: http://www.justice.gov/opa/pr/2012/July/12-civ-842.html).
[4] Office of Public Affairs, Department of Justice, "Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses" (2013) (available at: http://www.justice.gov/opa/pr/2014/February/14-civ-187.html).
[5] *Id*.

Court of Appeals for the Second Circuit has been the only circuit to hold that truthful, non-misleading off-label promotion is protected under the First Amendment in *United States v. Caronia*.[6] However, as evidenced by the recent Johnson & Johnson and Endo Health Solutions settlements, the free speech defense introduced in *Caronia* does not seem to be too promising for pharmaceutical companies faced with allegations of off-label promotion.

When the United States Court of Appeals for the Second Circuit decided *United States v. Caronia* in December 2012, the case was hailed as a "landmark" decision.[7] Up until this decision, no court has held that off-label promotion by pharmaceutical and medical device manufacturers and their representatives was protected under the Free Speech Clause of the First Amendment. This defense was not available when the Food and Drug Administration ("FDA") prosecuted off-label promotion for violating the misbranding provisions of the Food, Drug and Cosmetic Act ("FDCA"). The defendant in *Caronia* was convicted of conspiring to introduce a misbranded drug, Xyrem, into interstate commerce in violation of the FDCA. On appeal, the defendant ultimately prevailed on the grounds that his off-label promotion of the drug was lawful and protected under the First Amendment. In a 2-1 decision, the Second Circuit held that prohibiting the lawful off-label marketing of a drug unconstitutionally restricted free speech. Further, it held that the misbranding provision does not prohibit off-label promotion. It was the

[6] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012). There are no statutes which expressly prohibit off-label promotion; Medical journals and physicians are not prohibited from off-label promotion. *See* Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1946 (2012)

[7] *See In Landmark Ruling, Court Reverses Conviction Involving Off-Label Promotion*, FDA LAW BLOG, THE OFFICIAL BLOG OF HYMAN, PHELPS & MCNAMARA, P.C. (Dec. 3, 2012), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/12/in-landmark-ruling-court-reverses-conviction-involving-off-label-promotion.html; Robert Radick, *Caronia And The First Amendment Defense to Off-Label Marketing: A Six-Month Re-Assessment*, FORBES MAG. (May 29, 2013, 12:05 PM), http://www.forbes.com/sites/insider/2013/05/29/caronia-and-the-first-amendment-defense-to-off-label-marketing-a-six-month-re-assessment/.

first Federal Court of Appeals that interpreted the FDCA's misbranding provision to not expressly prohibit off-label promotion.

The Second Circuit's decision in *Caronia* relied on the Supreme Court's holding *Sorrell v. IMS Health, Inc.* In *Sorrell*, the Supreme Court recognized that pharmaceutical speech is commercial speech and therefore, is protected under the First Amendment. The Second Circuit took it one step further and held that lawful off-label promotion of drugs is also protected speech. The decisions in *Sorrell* and in *Caronia* appear to show an expansion in commercial speech rights in the context of pharmaceutical and medical device marketing. However, based on case law following the *Caronia* decision, it is unlikely that the decision will have a significant impact on off-label promotion. Moreover, it does not appear that the decision will affect government litigation tactics or enforcement efforts; numerous pharmaceutical manufacturers have pled guilty to allegations of violating the FDCA by promoting off-label uses and have settled with the government.

This Note will address whether the Second Circuit decision in *Caronia* has made an impact on off-label litigation in other circuits and within the circuit itself. In addition, the Note will focus on whether, as a response to the Second Circuit's decision, the Federal Government will change its strategies and tactics to enforce the misbranding provisions of the FDCA. It will be argued that pharmaceutical manufacturers are doubtful of the power and persuasiveness of the decision in *Caronia* and thus, are unwilling to assert the free speech defense in off-label prosecutions. Furthermore, this Note will assert that despite the expansion of pharmaceutical speech following *Sorrell* and *Caronia*, the Second Circuit's decision has had a limited persuasive impact on other circuits. This is because pharmaceutical companies do not believe that they are shielded from liability based on First Amendment protection. As a response, the federal

government has not changed its litigation strategies. In addition, the government will continue to hold that off-label promotion violates the misbranding provisions of the FDCA.

Part I of this Note will discuss the background of the Food, Drug and Cosmetics Act and the misbranding provisions. This section will conclude with a discussion of the views of the FDA regarding off-label use and promotion. Part II of this Note focuses on the First Amendment right to free speech and the evolution of commercial speech. Part III covers an analysis of *United States v. Caronia*. Part IV addresses the implications of the *Caronia* decision and will include a circuit-by-circuit review of cases which have cited to the Second Circuit's decision. Part V will analyze the effect of the decision on prosecution of off-label promotion under the FDCA by discussing settlements for off-label promotion against pharmaceutical manufacturers. Part VI will be the conclusion; it will summarize the conclusions of the Note and will introduce an alternative prosecution tactic against pharmaceutical companies for consideration.

Part I: Food, Drug and Cosmetic Act and Off-Label Promotion

Before entering interstate commerce, new drugs are subject to approval from the Food and Drug Administration to be marketed for specific uses.[8] Once a drug is approved by the FDA, physicians are free to prescribe it for approved and unapproved, or "off-label, uses."[9] Under the Food, Drug and Cosmetic Act ("FDCA"), introducing any adulterated or misbranded drug into interstate commerce is prohibited.[10] A drug is considered misbranded if its label does not bear

[8] 21 U.S.C. § 355 (a).
[9] U.S. Food and Drug Administration, "Use of Approved Drugs for Unlabeled Indications", 12 FDA drug bulletin 4 (April 1982)
[10] 21 U.S.C. § 331 (a).

adequate directions for use.[11] "Adequate directions for use" is defined as directions under which laypersons "may use the drug safely and for the purposes for which it is intended."[12]

"Off-label use" refers to the use of a drug, or other product, in a way that is not indicated on its FDA-approved label.[13] This term is applied when a drug is used to treat a disease not indicated on the FDA-approved label. The term is also applied when treating the indicated disease but prescribing the drug for a different dosage or prescribing it to a different patient population than indicated on the FDA-approved label.[14] Contrary to popular belief, off-label use is not itself a "risk" and not all off-label use is experimental.[15]

The FDA has conflated the definition of "off-label promotion" with "misbranding" and has prosecuted pharmaceutical companies for off-label conduct alone; the two terms are used interchangeably.[16] Following the 2012 decision in *United States v. Caronia*, the Federal Government has explained that off-label use is only *evidence* of misbranding.[17] It argues that promoting an off-label use is evidence that the speaker is asserting an intended use. Because it is off-label, the labeling of the drug does not bear adequate directions for this off-label use. "Intended uses" is defined as the "objective intent of persons legally responsible for the labeling of drugs."[18] This objective intent may be evidenced by a person's expressions by "labeling claims, advertising matter, or oral or written statements by such persons or their

[11] 21 U.S.C. § 352 (f).
[12] 21 C.F.R. § 201.5.
[13] Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 Am. Crim. L. Rev. 1945, 1946 (2012).
[14] James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconception*, 53 Food Drug L.J. 71, n.2 at 71 (1998) (citing William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 Food & Drug L.J. 247, 248 (1993)).
[15] *Id* at *72.
[16] Office of Public Affairs, Department of Justice "Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, N.Y.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations (2012).
[17] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
[18] 21 C.F.R. 201.128.

representatives."[19] Evidence of objective intent may also be shown by the circumstances surrounding the distribution of the product, such as whether it was offered and used for a purpose that was not labeled or advertised.[20]

While off-label promotion has been conflated with misbranding, the prohibition against off-label promotion is mainly directed at pharmaceutical and medical device manufacturers and their agents.[21] Other individuals and entities, such as medical journals and ordinary persons, are permitted to express whatever ideas and opinions they have about off-label use.[22] With these speakers, their promotion and discussions of off-label use has been acknowledged by the FDA to be of "high value" in the practice of medicine.[23] Off-label uses of drugs and medical devices are important in many areas of medicine, which "may account for more than 25 percent of approximately 1.6 billion prescriptions written each year with some recent estimates running as high as 60 percent."[24] The FDA has acknowledged that under certain circumstances, off-label use may be appropriate.[25] Such usage may even constitute a medically necessary standard of care.[26] The FDA has expressed reluctance to interfere with the practice of medicine or create barriers to physicians exercising their best judgment when considering treatment options for patients.[27] The FDCA expressly states that none of the provisions of the Act "shall be construed

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[19] *Id*.
[20] *Id*.
[21] Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1946 (2012).
[22] *Id* (quoting Ralph F. Hall & Elizabeth S. Sobotka, Comment, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 FOOD & DRUG L.J. 1., 8 (2007).
[23] Weaver v. Reagen, 886 F.2d 194, 198 (8th Cir. 1989).
[24] *Id* at *78 (quoting Lars A. Noah, Constraints on Off-Label Uses, 16(2) J. PROD & TOXICS LIAB. 139, 139 (1994).
[25] U.S. Food and Drug Administration, *FDA Drug Bulletin*, 12 FDA Drug Bull. 1, 5 (1982).
[26] U.S. Food and Drug Administration, *Draft Guidance, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publication on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2009).
[27] Weaver, 886 F.2d at 198.

to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health-care-practitioner-patient relationship."[28]

Off-label use has been connected to treatments for medical conditions such as "cancer, heart and circulatory disease, AIDS, kidney diseases requiring dialysis, osteoporosis, spinal fusion surgery, and various uncommon disease."[29] In addition, a majority of the drugs prescribed or administered to children are off-label because of the absence of clinical studies involving children.[30] Judicial courts have even recognized the public value of using drugs for appropriate off-label uses.[31] The Supreme Court stated that the off-label use of medical devices "is an accepted and necessary corollary of the FDA's mission to regulate this area without directly interfering with the practice of medicine."[32] The medical and scientific community has also recognized the importance of off-label use.[33]

While the FDA has given medical practitioners wide discretion in off-label use and promotion, the promotion of off-label uses of drugs by manufacturers and their representatives is not as freely accepted. Although the FDCA and its provisions do not expressly prohibit off-label statements, marketing and promotional statements by pharmaceutical companies and representatives can be evidence of a drug's intended use and therefore, proof of an intended use that was not FDA-approved.[34] The government has been adamant about prosecuting

[28] 21 U.S.C. § 396.
[29] *Id* (citations omitted).
[30] *Id* n. 81 (citing ROBERT LEVINE, ETHICS AND REGULATION OF CLINICAL RESEARCH 239 (2d ed. 1986).
[31] *See* Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001).
[32] Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 351 (2001).
[33] James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconception*, 53 FOOD DRUG L.J. 71, 78 (1998).
[34] 21 C.F.R. §201.5

manufacturers and their representatives for off-label promotion.[35] The FDA issued 42 regulatory notices and demanded that a number of drug manufacturers cease circulating information about off-label uses between 2003 to 2007.[36] During this time period, the Department of Justice settled eleven criminal and civil cases involving off-label promotion.[37]

Part II: Free Speech and the Evolution of Commercial Speech

Commercial speech is speech that advertises something of an economic nature.[38] It is related to a transaction involving the economic interests of the speaker and the listener.[39] Generally, commercial speech is given a lot of protection under the Constitution, but it is given less protection than content-based speech.[40] However, if the commercial speech is false and misleading, it is not protected under the First Amendment, and the government has the right to punish the speaker.[41] The government also has the power to regulate truthful, non-deceptive commercial speech, such as gambling, liquor ads, and lawyer ads.[42] Prior to 1976, commercial speech was not protected under the First Amendment.[43] However, in *Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council* the Supreme Court reversed the decision in *Valentine v. Crestensen* and held that under the First Amendment, the public has the right to receive information regarding the prices of prescription drugs through advertising and other

[35] Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 Am. Crim. L. Rev. 1945, 1946 (2012).
[36] U.S. Gov't Accountability Office, Highlights, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses (July 2008).
[37] *Id*.
[38] Valentine v. Chrestensen, 316 U.S. 52 (1942).
[39] *Id*.
[40] Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, 425 U.S. 748 (1976).
[41] *See* Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, 425 U.S. 748 (1976).
[42] *See* Greater New Orleans Broad. Ass'n v. United States, 527 U.S. 173 (1997); 44 Liquormart, Inc. v. R.I., 517 U.S. 484 (1996); Shapero v. Kentucky Bar Ass'n, 486 U.S. 466 (1988).
[43] *See* Valentine v. Chrestensen, 316 U.S. 52 (1942).

promotional methods.[44] The Court held that this information was valuable and even though it was "commercial," it was "of general public interest."[45] The public has the right to be well-informed in order to make intelligent decisions[46]; therefore, there must a "free flow of commercial information."[47]

The Supreme Court then introduced a four-prong test to guide the courts in determining whether the commercial speech at issue is protected under the First Amendment.[48] First, the speech must concern lawful activity and must not be misleading; second, there must be a substantial government interest; third, the regulation must advance the government interest; and finally, the fit between the legislative ends and means to accomplish this must be narrowly tailored.[49] In *44 Liquormart, Inc. v. R.I.*, the Supreme Court held that Rhode Island did not have the broad discretion to suppress truthful, non-misleading information for paternalistic purposes.[50] The Court held that the dissemination of truthful and non-misleading commercial information pertaining to lawful products and services was protected under the First Amendment.[51] Specifically, these types of messages are accorded strict scrutiny; "unlike content-neutral restrictions on time, place, or manner of expression," complete speech bans preclude alternative modes of disseminating information and thus, they require a more rigorous form of review.[52]

Moreover, in *Lorillard Tobacco Co. v. Reilly*, the Supreme Court found that the government had a substantial interest in preventing underage smoking, but the sale and use of

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[44] *Id*.
[45] *Id* at 764.
[46] *Id* at 765.
[47] *Id*.
[48] Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm'n, 447 U.S. 557, 566 (1980).
[49] *Id*.
[50] 517 U.S. 484, 489 (1996).
[51] *Id* at 496.
[52] *Id* at 501.

tobacco products by adults is legal.[53] The Attorney General failed to prove that the outdoor advertising ban was not more extensive than necessary, under the fourth prong of the *Central Hudson* test.[54] The Court held that the public has an interest in receiving this information.[55]

The Supreme Court has expanded corporate free speech rights in the context of pharmaceutical speech—the level of protection has increased and the scope of activity defined as "speech" has broadened.[56] In *Thompson v. Western States Medical Center*, Congress enacted the Food and Drug Administration Modernization Act; this Act exempted compounded drugs from the FDA drug approval process if the drug providers did not advertise them.[57] The Supreme Court held that the advertising restriction was unconstitutional.[58] The trend in the history of commercial speech appears to be constantly expanding what qualifies as commercial speech and to allow advertising if it is truthful and non-misleading.[59]

In 2011, the Supreme Court held that pharmaceutical speech is protected under the First Amendment.[60] The decision in *Sorrell v. IMS Health, Inc.* shows an expansion of commercial speech because the Supreme Court found that speech relating to information and pricing of pharmaceuticals was a form of commercial speech.[61] The expansion of the definition of commercial speech is evidence that the Supreme Court continues to be highly protective of commercial speech.

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[53] 533 U.S. 525 (2001).
[54] *Id*.
[55] *Id*.
[56] Thompson v. Western States Medical Center, 535 U.S. 357 (2002; Sorrell v. IMS Health, Inc. 131 S. Ct. 2653 (2011).
[57] 535 U.S. 357, 360 (2002)
[58] *Id*.
[59] *Id*.
[60] *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670 (2011). *See infra* Part III for a discussion of the facts and holding of Sorrell v. IMS Health Inc.
[61] Sorrell, 131 S. Ct. at 2672.

Part III: Analysis of *United States v. Caronia*

The Supreme Court's decision in *Sorrell v. IMS Health, Inc.* represents an expansion of commercial free speech rights for two reasons. First, the level of protection offered has increased.[62] Second, the scope of activity defined as "speech" was broadened in the context of pharmaceutical speech.[63] Subsequently, the Second Circuit's decision in *United States v. Caronia* was heavily influenced by the Supreme Court's decision in *Sorrell*. There, the Supreme Court held that pharmaceutical marketing constitutes speech that is protected under the First Amendment.[64] The Supreme Court found that the Vermont Law, § 4631(d), which barred pharmaceutical manufacturers and representatives from using prescriber-identifiable information for marketing or promoting a drug, violated the First Amendment.[65] The Court utilized a two-part test to reach its holding, which first asks whether the law enacted content-based and speaker-based restrictions. Next, the Court applied the *Central Hudson* four-part test.[66] The Vermont legislation was found to be a content-based restriction because it disfavored pharmaceutical marketing; the speech was barred if it was used for marketing but not if it was used for educational communications.[67] The *Sorrell* Court found it was also a speaker-based restriction because it barred only pharmaceutical manufacturers and representatives—specifically detailers—from communicating the information.[68] The two-part test utilized by the Supreme Court was ultimately adopted by the Second Circuit in *United States v. Caronia*.[69]

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[62] Seth E. Mermin & Samantha K. Graff, *The First Amendment and Public Health, At Odds*, 39 Am. J. L. and Med. 298, 299 (2013).
[63] *Id*.
[64] Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670 (2011).
[65] *Id* at 2672.
[66] *Id* at 2663-2672.
[67] *Id* at 2663.
[68] *Id*.
[69] 703 F.3d 149, 163 (2012).

In *United States v. Caronia*, the United States District Court for the Eastern District of New York convicted a pharmaceutical sales representative, Alfred Caronia, of introducing a misbranded drug, Xyrem, into interstate commerce.[70] Xyrem is a sleep-inducing depressant that was first approved in July 2002 to treat cataplexy, a condition associated with narcolepsy.[71] In November 2005, the drug was approved to treat excessive daytime sleepiness in patients suffering from narcolepsy.[72] The active ingredient in Xyrem is gamma-hydroxybutryate ("GHB"),[73] and the drug has been found to have serious potential side effects.[74] The claims against Caronia arise from interactions with two physicians. To one physician, Caronia informed him that Xyrem could be used to treat fibromyalgia, muscle disorders, chronic pain and fatigue—all of which are off-label uses.[75] To another physician, Caronia recommended the drug not only for fibromyalgia, but also for sleepiness, weight loss and chronic fatigue, which are off-label uses as well .[76]

Caronia was found guilty of misbranding Xyrem by promoting its off-label uses in violation of the misbranding provisions of the Federal Food, Drug and Cosmetics Act.[77] Caronia appealed the conviction, and the United States Court of Appeals for the Second Circuit reversed and vacated the conviction.[78] The Second Circuit held that Caronia's off-label promotion of Xyrem was protected under the Free Speech Clause of the First Amendment.[79] Further, the Court held that the government prosecution of pharmaceutical companies and their agents for the

[70] 576 F. Supp. 2d 385 (E.D.N.Y. 2008).
[71] *Id* at 388.
[72] *Id* at 388-389.
[73] *Id* at 388.
[74] *Id* at 389.
[75] *Id*.
[76] *Id* at 390.
[77] *Id*.
[78] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
[79] *Id*.

promotion of truthful, non-misleading off-label uses of a drug was a violation of their First Amendment rights.[80]

The Court in *Caronia* used the Supreme Court's decision in *Sorrell*, which was decided after the Eastern District of New York convicted Alfred Caronia, in order to guide its decision. Applying the two-part test introduced in *Sorrell*, the Second Circuit found that Caronia's off-label promotion to the two physicians was protected under the First Amendment. The Court found that making off-label promotion unlawful is a content-based restriction because it criminalizes only speech that concerns unapproved uses.[81] In addition, it is a speaker-based restriction because it criminalizes the speech only when the speaker is a pharmaceutical representative or agent not when it is a physician.[82] Applying the *Central Hudson* four-part test, the Court found that the Government had substantial interests in protecting the public from possibly unsafe and ineffective drugs.[83] However, preventing a class of people, namely, the pharmaceutical companies and their representatives, from engaging in truthful off-label promotion of drugs would not directly further these government interests.[84] Finally, the Court held that the government's regulation was not narrowly tailored to achieving the interests asserted because it was more extensive than necessary.[85]

The decisions in *Sorrell* and *Caronia* show an expansion in the commercial free speech doctrine because the definition of "commercial speech" includes pharmaceutical speech, and this

[80] *Id*.
[81] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
[82] *Id*.
[83] *Id* at 166.
[84] *Id*.
[85] *Id* at 167.

speech is protected under the First Amendment.[86] The *Caronia* decision was hailed as a landmark case that gave rise to a circuit split between the Second Circuit and every other Federal Circuit because the Second Circuit was the only one to hold that off-label promotion was protected free speech under the First Amendment. The decision was likely regarded as a "landmark" decision because it created a Constitutional defense for pharmaceutical manufacturers and their agents in actions alleging violation of provisions of the FDCA based on off-label promotion. Until the Second Circuit's decision in *Caronia* it appeared that the FDA enjoyed immense power in the enforcement of the misbranding provisions and the prosecution of off-label promotion as evidenced by the large settlements against pharmaceutical companies.[87] Some pharmaceutical manufacturers have relied on *Caronia* to to assert the Free Speech defense that their off-label marketing was constitutionally protected and did not violate the FDCA. It is now apparent that "landmark" was too ambitious of a word to describe the *Caronia* decision; this defense has not been universally successful in all cases where it was asserted.[88]

Part IV: Implications of *Caronia*

Since the Second Circuit's decision in 2012, some pharmaceutical manufacturers have asserted that off-label marketing is constitutionally protected speech and is not a violation of the FDCA. This defense, however, has not been universally successful.[89] Some courts adopted the *Caronia* decision,[90] while others found it nonpersuasive.[91]The *Caronia* decision demonstrates an

[86] Mark J. Scheineson & Guillermo Cuevas, *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 FOOD DRUG L.J. 201 (2013).
[87] *See* Katherine A. Blair, *In This Issue, In Search of the Right R[x]: Use of the Federal False Claims Act in Off-Label Drug Promotion Litigation*, 23 HEALTH LAWYER 44 (2001).
[88] *See infra* Part IV.
[89] *See infra* Part IV.
[90] *See* Dawson v. Medtronic, Inc., No. 2:13-cv-663-JFA, 2013 U.S. Dist. LEXIS 112877, at *2 (D.S.C. 2013); Otis-Wisher v. Fletcher Allen Health Care, Inc., 2013 U.S. Dist. LEXIS 88813, at *17 (D. Vt. 2013); Gavin v. Medtronic,

expansion in commercial speech rights in the context of pharmaceutical and medical device marketing, but the case law following the decision suggests the decision will not significantly impact off-label promotion.

Although the defendant in *Caronia* was a sales representative for a *pharmaceutical* company, the decision of the Second Circuit has been used exclusively by *medical device* companies as a defense during litigation. pharmaceutical drugs, Medical device manufacturers, like pharmaceutical manufacturers, must abide by the provisions of the FDCA and follow FDA regulations and procedures. Nonetheless, there are differences in FDA processes for new drug approval and for new medical device approval for marketing and use in interstate commerce.

New drugs undergo three stages of clinical testing via the Investigational New Drug ("IND") process.[92] If testing concludes that a drug is safe and effective, the manufacturer can submit a New Drug Application ("NDA").[93] The FDA often approves or clears new drugs with the knowledge that the drugs will likely used for off-label indications, especially when the practice of good medicine requires that a physician use drugs "according to [his] best knowledge and judgment.[94]

There a two ways in which the FDA approves the marketing of a new medical device; the medical device can receive 510(k) clearance or it can receive premarket approval. 510(k) is a premarketing submission to the FDA that a device is substantially equivalent to a legally

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Inc., 2013 U.S. Dist. LEXIS 101216, at *15 (E.D. La 2013); Lawrence v. Medtronic, Inc., 2013 Minn. Dist. LEXIS 3 (Minn. Dist. Ct. 2013).

[91] *See* Ramirez v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 118822 (D. Ariz. 2013); Carson v. Depuy Spine, Inc. 365 Fed. App'x 812, 815 (9th Cir. 2010); McDonald-Lerner v. Neurocare Assocs, P.A., No. 373859-V, 2013 Md. Cir. Ct. LEXIS 6, at *3 (Md. Cir. Ct. 2013).

[92] *Id* at 73.

[93] *Id*.

[94] *Id*.

marketed device.[95] A medical device receives 510(k) clearance if the product can be demonstrated to be substantially equivalent to a device that either was in distribution prior to the Medical Device Amendments of 1976 (MDA), or was grandfathered in statutorily, or was otherwise being marketed legally.[96] The "vast majority of devices" are cleared by the FDA through this 510(k) process because the history of other substantially equivalent devices is an indication of its safety and effectiveness.[97]

The premarket approval (PMA) process is lengthier and more rigorous than the 510(k) process because there is "no history of equivalent predicate device to serve as an indicator of safety and effectiveness."[98] Not only is this process more complicated, but it is also more costly to device manufacturers and can take years before it is FDA-approved.[99] Additionally, a medical device manufacturer can also seek an exemption by applying for an Investigational Device Exemption (IDE), which is a process that allows otherwise unapproved medical devices products to be used to investigate the safety and effectiveness of the product.[100]

Three federal courts in the Second, Fourth, and Fifth Circuits, and a Minnesota state court have adopted the holding in *Caronia* that the FDCA does not expressly prohibit off-label promotion.[101] Courts in these jurisdictions have reiterated that off-label promotion is not a violation of the FDCA. However, other jurisdictions have held that off-label promotion is a violation of the Act. The Ninth Circuit follows circuit precedence and continues to hold that off-

[95] Pub. L. No. 94-295, 90 Stat. 539 (1976).
[96] *Id*.
[97] James M. Beckel & Elizabeth Azari, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food Drug L.J. 71, 73 (1998) (citing Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996).
[98] *Id*.
[99] *Id*.
[100] *Id*.
[101] *See* Otis-Wisher v. Fletcher Allen Health Care, Inc., 2013 U.S, Dist. LEXIS 88813 (D. Vt. 2013). *See also* Dawson v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 112877 (D.S.C. 2013). *See also* Gavin v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 101216 (E.D. La. 2013). *See also* Lawrence v. Medtronic, Inc. 2013 Minn. Dist. LEXIS 3 (Minn. Dist. 2013).

label promotion is a violation of the misbranding provisions of the FDCA.[102] A Maryland state court agrees with the dissent in *Caronia* and refuses to hold that off-label promotion is not prohibited under the FDCA.[103]

Recently, Medtronic, Inc. has faced numerous lawsuits involving its InFuse Bone Graft/LT-Cage Lumbar Tapered Fusion Device ("InFuse Device). As a defense, the medical technology company has utilized the Second Circuit's holding that off-label promotion does not violate the FDCA. The InFuse Device is a Class III device manufactured and marketed by Medtronic, Inc., a medical technology company. The InFuse device consists of three components: a recombinant human bone morphogenetic protein-2 ("rhBMP-2"), an absorbable collagen sponge, and an interbody fusion device.[104] The device was approved by the FDA after the FDA conducted its rigorous premarket approval ("PMA") process.[105] The device is implanted into the vertebrae and has been approved by the FDA for anterior insertion through the abdomen.[106]

The plaintiffs in the InFuse Device lawsuits against Medtronic, Inc. contended that it was the off-label promotion by Medtronic representatives to physicians that induced the physicians to perform their spinal fusion surgeries using off-label methods.[107] Specifically, the plaintiffs allege that the representatives encouraged the surgeons to implant only one component in the InFuse Device system, instead of all three components, and to use a posterior approach during surgery,

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[102] Eidson v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 144179 (N.D.Calif. 2013); Ramirez v. Medtronic Inc., 2013 U.S. Dist. LEXIS 118822 (D. Ariz. 2013).
[103] McDonald-Lerner v. Neurocare Assocs, P.A., No. 373859-V, 2013 Md. Cir. Ct. LEXIS 6, at *3 (Md. Cir. Ct. 2013).
[104] Dawson v. Medtronic, Inc., No. 2:13-cv-663-JFA, 2013 U.S. Dist. LEXIS 112877, at *2 (D.S.C. 2013).
[105] *Id*.
[106] McDonald-Lerner, 2013 Md. Cir. Ct. at *3.
[107] Dawson, 2013 U.S. Dist. LEXIS 112877 (D.S.C. 2013); Otis-Wisher, 2013 U.S. Dist. LEXIS 88813 (D. Vt. 2013); Gavin, 2013 U.S. Dist. LEXIS 101216 (E.D. La 2013); Lawrence, 2013 Minn. Dist. LEXIS 3 (Minn. Dist. Ct. 2013); Ramirez, 2013 U.S. Dist. LEXIS 118822 (D. Ariz. 2013); Carson, 365 Fed. App'x 812 (9th Cir. 2010); McDonald-Lerner, 2013 Md. Cir. Ct. LEXIS 6 (Md. Cir. Ct. 2013).

rather than the FDA-approved anterior approach.[108] Plaintiffs claim that the off-label promotion of the device was executed without fully disclosing all the adverse effects and risks of the off-label uses.[109] The plaintiffs further assert that these two off-label approaches caused them to suffer from resultant injuries.[110] These injuries range from severe bone growth, pain, numbness, and difficulties with certain motor function.[111]

Several United States District Courts, and a Minnesota state court have followed the Second Circuit's decision. These courts have held that off-label promotion is not unlawful under the misbranding provision of the FDCA, and subsequently rejected the off-label promotion and use claims asserted by plaintiffs. The courts eventually recognized that the FDCA does not prohibit all promotion of off-label uses.[112]The United States District Courts and the Minnesota state court identified *Buckman Co. v. Plaintiff's Legal Comm*. as binding authority. The Supreme Court held that physicians are able to prescribe drugs and devices for off-label uses.[113] Moreover, the Court recognized the importance of not interfering with the practice of medicine and allowing doctors to prescribe drugs and devices for uses that have not been approved by the FDA.[114]

In the above referenced InFuse Device cases, the plaintiffs failed to establish a link between off-label promotion and their alleged injuries. They could not state specific statements made by Medtronic, Inc. or its agents, which induced the surgeons to use the Infuse Device and perform the surgery in an off-label way. Since plaintiffs could not identify specific instances of

[108] *See* cases cited *supra* note 104.
[109] *See* cases cited *supra* note 104.
[110] *See* cases cited *supra* note 104.
[111] *See* cases cited *supra* note 104.
[112] *See* cases cited *supra* note 104.
[113] 531 U.S. 341 (2001).
[114] *Id*.

off-label promotion to the surgeons, these courts adhered to the Supreme Court presumption in *Buckman* that physicians have the discretion to use drugs and medical devices in off-label ways as long as they are an appropriate course of treatment.[115]

In *Dawson v. Medtronic, Inc.* the United States District Court for the District of South Carolina, in the Fourth Circuit, rejected plaintiff's claim that off-label promotion was illegal under the FDCA.[116] Because the Court refused to accept this assertion, plaintiff failed to specify what other federal law the off-label promotion allegedly conducted by Medtronic would be violating.[117] Additionally, the Court held that if state law proscribed such conduct, it would be preempted because it is not unlawful under traditional state tort law.[118]

Following the decision of *Caronia*, a court in the Second Circuit followed circuit precedence and held that off-label promotion is not unlawful under the Food, Drug and Cosmetics Act. The District Court for Vermont held that because the claims against Medtronic, Inc. failed to identify the specific federal requirement violated under the Act, the claims were preempted.[119] The District Court acknowledged that misbranding is criminal under the FDCA, but the plaintiff in this case did not allege any misbranding.[120] She failed to plead with particularity since "bare bones allegations do not satisfy Rule 9(b)."[121]

In *Gavin v. Medtronic, Inc.*, the plaintiff in this case also did not satisfy the requirement for the claim to escape preemption because plaintiff could not assert a parallel claim that was

[115] 531 U.S. 341 (2001).
[116] Dawson v. Medtronic, Inc., No. 2:13-cv-663-JFA, 2013 U.S. Dist. LEXIS 112877, at *2 (D.S.C. 2013).
[117] *Id*.
[118] *Id*.
[119] Otis-Wisher v. Fletcher Allen Health Care, Inc., 2013 U.S. Dist. LEXIS 88813, at *17 (D. Vt. 2013)
[120] *Id* at *15.
[121] *Id*.

pled with particularly.[122] Specifically, plaintiff did not explain how violating the federal requirement caused his alleged injuries. The United States District Court for the Eastern District of Louisiana specified that under §360(k), the question is not "whether there are federal requirements applicable to a *particular use* of a device," but rather "whether there are federal requirements applicable to *the device*" (emphases in the original).[123] The decision further explained that neither the language of §360(k)(a) or the Supreme Court's decision in *Riegel v. Medtronic, Inc.* suggested that preemption depends on how the device is promoted.[124]

A Minnesota state court adopted the holding in *Caronia* when the plaintiffs in the case sought judgment against Medtronic, Inc.[125] The plaintiffs alleged that defendant Medtronic, Inc. and its agents promoted the off-label use of the InFuse system by illegally inducing surgeons to only one component of the three-component InFuse system.[126] This off-label use allegedly resulted in injury to the plaintiffs and required them to undergo additional surgeries.[127] The Minnesota District Court conceded with the majority in *Caronia* that federal law does not prohibit all promotion of off-label uses.[128]

Medtronic, Inc. has not been equally successful when asserting the *Caronia* decision as a defense in other jurisdictions. In 2010, the United States Court of Appeals for the Ninth Circuit held that off-label promotion is illegal under the provisions of the FDCA.[129] Following the Second Circuit's decision in 2012, two district courts in the Ninth Circuit followed their circuit precedent and found that off-label promotion by Medtronic, Inc. was illegal under the

[122] Gavin v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 101216, at *15 (E.D. La 2013).
[123] *Id* at *34 (citing Caplinger, 2013 U.S. Dist. LEXIS 16047, at *10).
[124] *Id*.
[125] Lawrence v. Medtronic, Inc., 2013 Minn. Dist. LEXIS 3 (Minn. Dist. Ct. 2013).
[126] *Id*.
[127] *Id*.
[128] *Id*.
[129] Carson v. Depuy Spine, Inc. 365 Fed. App'x 812, 815 (9th Cir. 2010).

FDCA.[130]Medtronic attempted to rely on the interpretation of the misbranding provision in *Caronia*, but the argument was ultimately struck down by the United States District Court for the District of Arizona and the United States District Court for the Northern District of California, which are not bound the Second Circuit.[131] The two district courts held that the FDA has construed the FDCA as prohibiting off-label promotional speech as misbranding itself, and the Ninth Circuit remains deferential to the decisions of the FDA.[132]

In a case brought before the Circuit Court of Maryland, a state court, Medtronic Inc. again relied on the Second Circuit's decision in *Caronia* and contended that off-label use and promotion is neither illegal nor improper under the FDCA.[133] The Circuit Court of Maryland found that the majority opinion in *Caronia* was unpersuasive, and thus, it "decline[d] to follow the reasoning of the . . . majority."[134] The Maryland state court instead agreed with the dissenting judge in *Caronia* that finding that off-label promotion is not a violation of the FDCA would frustrate the purpose of the FDA's stringent labeling regulations and premarket approval process for drugs.[135] The court went on to find that this purpose would be compromised by allowing manufacturers and their sales representatives to have broad discretion to promote off-label uses to physicians.[136]

Although the adoption of the *Caronia* holding in the Fourth and Fifth Circuit, as well as in a Minnesota state court would appear to be evidence of the persuasiveness of the holding in

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[130] *See* Ramirez v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 118822 (D. Ariz. 2013).
[131] *See* Ramirez v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 118822 at *49; *see also* Eidson v. Medtronic, 2013 U.S. Dist. LEXIS 144179 (N.D. Calif. 2013).
[132] Ramirez v. Medtronic, Inc., 2013 U.S. Dist. LEXIS 118822 (D. Ariz. 2013); Eidson v. Medtronic, 2013 U.S. Dist. LEXIS 144179 (N.D. Calif. 2013). *See* Carson v. Depuy Spine, Inc. 365 Fed. App'x 812, 815 (9th Cir. 2010).
[133] McDonald-Lerner v. Neurocare Assocs., P.A., No. 373859-V, 2013 Md. Cir. Ct. LEXIS 6, at *3 (Md. Cir. Ct. 2013).
[134] *Id* at *22.
[135] *Id* at *23.
[136] *Id*.

Caronia, this is not the opinion held by all courts. The Ninth Circuit decisions in a number of InFuse Device cases, and a decision by a Maryland state court reveal that the Second Circuit's is neither binding nor persuasive on courts outside that circuit. Moreover, off-label promotion can continue to be illegal under the provisions of the FDCA.

Part V: Effect of *Caronia* on Government Prosecution of Off-label Promotion

The first pharmaceutical off-label settlement post-*Caronia* involved Pfizer Inc. for misbranding its drug, Protonix.[137] On December 12, 2012, just days after the *Caronia* decision, Pfizer agreed to pay $55 million in order to resolve allegations that Wyeth L.L.C. introduced the misbranded drug into interstate commerce.[138] Protonix has FDA-approval to treat short-term erosive esophagitis.[139] However, the United States alleged that the Pfizer intended to and did promote the drug for *all* forms of gastro-esophageal reflux disease ("GERD").[140] The FDA warned Wyeth that its proposed promotional materials were misleading because the company was overstating the uses for which the drug was actually approved by suggesting that it was safe for treating GERD.[141] In its complaint, the government alleged that Wyeth ignored the FDA warning notice by actively training its sales force to promote the drug for all forms of GERD.[142] Furthermore, the government contended that Wyeth promoted Protonix as the "best" for nighttime heartburn despite the lack of clinical evidence that it has superior efficacy over other

[137] Office of Public Affairs, Department of Justice, "Pfizer Agrees to Pay $55 Million for Illegally Promoting Protonix for Off-Label Use" (2012).
[138] *Id*. Wyeth L.LC. was a pharmaceutical company purchased by Pfizer Inc. in 2009.;
[139] *Id*.
[140] *Id*.
[141] Wyeth L.LC. was a pharmaceutical company purchased by Pfizer Inc. in 2009.; Office of Public Affairs, Department of Justice, "Pfizer Agrees to Pay $55 Million for Illegally Promoting Protonix for Off-Label Use" (2012).
[142] *Id*.

products.[143] Finally, Wyeth was allegedly using continuing medical education programs as a vehicle to promote Protonix for off-label uses.[144]

Within the same month of *Caronia,* Amgen, Inc. settled with the federal government and pled guilty before the United States District Court for the Eastern District of New York to illegally introducing the misbranded drug, Aranesp, into interstate commerce.[145] In addition, it agreed to pay $762 million to resolve criminal and civil liability from the sale and promotion of certain drugs.[146] The drug was approved by the FDA at certain doses for particular patient populations suffering from anemia, but in order to increase its profits, Amgen, Inc. promoted it for a dosage that was rejected by the FDA.[147] The government alleged that to the company instructed its sales representatives in "reactive marketing" by inducing doctors to ask about off-label uses.[148] This tactic was used to ensure the company did not outwardly promote the drugs for off-label uses and thus, would not violate the misbranding provision of the FDCA.[149] Because this action was brought before the Eastern District of New York, the *Caronia* decision would have been binding on this court. However, Amgen, Inc. did not attempt to assert the Free Speech defense, nor did it attempt to argue that its off-label promotion of Aranesp was not prohibited by the FDCA.

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[143] *Id*.
[144] Wyeth L.LC. was a pharmaceutical company purchased by Pfizer Inc. in 2009.; Office of Public Affairs, Department of Justice, "Pfizer Agrees to Pay $55 Million for Illegally Promoting Protonix for Off-Label Use" (2012).
[145] Office of Public Affairs, Department of Justice, "Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations" (2012).
[146] *Id*.
[147] *Id*.
[148] *Id*.
[149] *Id*.

In its Megace ES settlement, Par Pharmaceuticals agreed to pay $45 million to resolve civil and criminal claims, and it pled guilty to misbranding Megace ES in violation of FDCA.[150] Megace ES was approved by FDA "to treat anorexia, cachexia, or other significant weight loss suffered by patients with AIDS."[151] The company was charged with misbranding because it promoted or intended to promote the drug for non-AIDS-related geriatric wasting which is a use not approved by the FDA.[152] The United States asserted that the company deliberately targeted elderly nursing home patients with weight loss, even though it was allegedly aware of the drug's adverse effects in elderly patients.[153] The United States further contended that the company made substantiated and misleading representations about their drug in order to encourage providers to prescribe Megace ES over the generic alternative;[154] the company had no well-controlled studies to substantiate their claims of the greater efficacy of their drug.[155]

Six months after the decision in *Caronia*, the Second Circuit encountered its second settlement against a pharmaceutical company for off-label promotion.[156] Before District Court for the Western District of New York, ISTA Pharmaceuticals, Inc. agreed to pay $33.5 million to resolve criminal and civil liability for conspiring "to introduce a misbranded drug into interstate commerce" with the intention that its drug, Xibrom, be promoted for unapproved uses.[157] Xibrom was FDA-approved to treat pain and inflammation following cataract surgery.[158] Some of the pharmaceutical representatives of ISTA Pharmaceuticals promoted the drug for use

[150] Office of Public Affairs, Department of Justice, "Par Pharmaceutical Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing" (2013).
[151] *Id*.
[152] *Id*.
[153] *Id*.
[154] [154] Office of Public Affairs, Department of Justice, "Par Pharmaceutical Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing" (2013).
[155] *Id*.
[156] Office of Public Affairs, Department of Justice, "ISTA Pharmaceuticals Inc. Pleads Guilty to Federal Felony Charges; Will Pay $33.5 Million to Resolve Criminal Liability and False Claims Act Allegations" (2013).
[157] *Id*.
[158] *Id*.

following Lasik and glaucoma surgeries and for the treatment of cystoid mascular edema.[159] ISTA pled guilty based on evidence that some of its employees were instructed not to leave a "paper trail" from interactions with physicians regarding unapproved new uses of the drug.[160] The government alleged that: ISTA employees promoted the drug for off-label uses; CME programs were used to promote uses that were not approved by FDA as safe and effective; and post-operative instruction sheets for off-label uses were paid for by company employees and given to physicians.[161] Similar to Amgen, Inc. in its Aranesp settlement, ISTA Pharmaceuticals also decided to settle with the government and plead guilty to allegations of off-label promotion rather than to assert *Caronia* as a defense.

In July 2013, Wyeth Pharmaceuticals Inc. paid $490.9 Million to resolve criminal and civil claims arising from unlawful marketing of its drug, Rapamune, for uses that were not approved by the FDA as safe and effective.[162] The drug received FDA-approval for use in kidney transplant patients.[163] However, the information alleged that the company promoted the drug to non-renal transplant patients.[164] The government also asserted that Wyeth provided its sale representatives with training material on off-label uses and instructed them how to present this material to physicians to increase.[165] Wyeth created financial incentives to the sales representatives, and it was evidence of valuing profit over consumer safety.[166]

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[159] Office of Public Affairs, Department of Justice, "ITSA Pharmaceuticals Inc. Pleads Guilty to Federal Felony Charges; Will Pay $33.5 Million to Resolve Criminal Liability and False Claims Act Allegations" (2013).
[160] *Id*.
[161] *Id*.
[162] Office of Public Affairs, Department of Justice, "Wyeth Pharmaceuticals Agrees to Pay $490.9 Million for Marketing the Prescription Drug Rapamune for Unapproved Uses" (2013).
[163] *Id*.
[164] *Id*.
[165] Office of Public Affairs, Department of Justice, "Wyeth Pharmaceuticals Agrees to Pay $490.9 Million for Marketing the Prescription Drug Rapamune for Unapproved Uses" (2013).
[166] *Id*.

Two months after Wyeth Pharmaceuticals Rapamune settlement, Abbott Laboratories, Inc. settled with U.S. Department of Justice for the promotion of its drug, Depakote, for unapproved uses.[167] The total settlement amount was $1.5 billion, which was the largest single-drug settlement of an off-label case up to that date.[168] Abbott Laboratories was prosecuted for the unlawful promotion for the drug for uses not approved as safe and effective by the FDA.[169] The drug company pled guilty to misbranding the drug.[170]On November 4, 2013, the Department of Justice reported that Johnson & Johnson agreed to pay more than $2.2 billion to resolve criminal and civil investigations.[171] The allegations against the health care giant included off-label promotion of the drugs, Risperdal, Invega, and Natrecor, and providing kickbacks to doctors and pharmacists.[172] This settlement was the second largest health care fraud settlement in United States history with criminal fines and forfeiture totaling $485 million, and with a civil settlement with the federal government and several states totaling $1.72 billion.[173] The statement by Attorney General, Eric Holder, that this settlement "demonstrates the Justice department's firm commitment to preventing and combating all forms of health care fraud," reveals that the FDA and the Department of Justice were not hindered by the Second Circuit's decision in *Caronia* in prosecuting off-label promotion.[174]

Finally, in the most recent off-label promotion settlement—and certainly not the last—Endo Health Solutions, Inc. ("Endo") and its subsidiary, Endo Pharmaceutical, Inc. paid $192.7

[167] The United States Attorney's Office, Western District of Virginia, "U.S. Attorney Heaphy Announces Distribution of Forfeiture Proceeds to Commonwealth's Attorneys: Local Prosecutors Supported Federal Prosecution of Abbott Laboratories" (2013).
[168] *Id*.
[169] *Id*.
[170] *Id*.
[171] Office of Public Affairs, Department of Justice, "Johnson & Johnson to Pay More Than $2.2 Billion to Resolve Criminal and Civil Investigations" (2013).
[172] *Id*.
[173] *Id*.
[174] *Id*.

million to settle criminal and civil claims arising from the off-label promotion of its drug, Liboderm.[175] The information alleges that Endo promoted the drug for the off-label uses of treating low back pain, diabetic neuropathy and carpal tunnel.[176] The drug was only FDA-approved to relieve pain associated with post-herpetic neuralgia, which is a complication of shingles.[177]The action against Endo was brought in the District Court for the Northern District of New York, which is within the jurisdiction of the Second Circuit. Not unlike, Amgen, Inc. and Wyeth pharmaceuticals, Endo chose to defer prosecution and settle with the government rather than assert the *Caronia* decision at trial. In regards to the settlement with Endo, Assistant Attorney General for the Justice Department's Civil Division, Stuart Delery, stated that the government "will hold accountable those who circumvent that process in pursuit of financial gain."[178] Assistant Attorney General Delery's statement reinforces the point that prosecution against pharmaceutical manufacturers for off-label promotion was not significantly impacted by the Second Circuit's decision in *Caronia*.

A tension exists between ensuring public health and mandating that drugs introduced into the marketplace are approved by the FDA. However, because physicians are not precluded from promoting off-label uses of drugs, a First Amendment free speech violation may exist owing to the fact that pharmaceutical manufacturers are not given the same freedom. The difference between these two groups is attributable to the presumption that physicians promote off-label uses to serve the best interests of the patient. In contrast, it is presumed that pharmaceutical

[175] Office of Public Affairs, Department of Justice, "Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses" (2013) (available at: http://www.justice.gov/opa/pr/2014/February/14-civ-187.html).
[176] *Id*.
[177] *Id*.
[178] Office of Public Affairs, Department of Justice, "Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses" (2013) (available at: http://www.justice.gov/opa/pr/2014/February/14-civ-187.html).

companies and their agents are motivated to promote off-label uses to increase profit, irrespective of the safety of the consumers. By promoting drugs for off-label uses, dosages, and non-approved patient populations, the drug companies can reach a broader range of consumers and thus, increase profits significantly. Although, speaker-based and content-based restrictions may exist when prosecuting a pharmaceutical company and its agents for off-label marketing, the safety and efficacy of a drug may will outweigh any interests in free speech rights.

Over a year has passed since *United States v. Caronia*. What was once hailed as a landmark decision, and what appeared to be an expansion in pharmaceutical speech, has had little persuasive effect on the prosecution of off-label drug promotion by pharmaceutical companies. The government has remained steadfast in its commitment to prosecute for violations under the misbranding provision of the FDCA and in targeting companies that promote drugs for uses that have not been approved by the FDA. Since *Caronia*, numerous pharmaceutical companies have settled with the government for allegations of misbranding through off-label promotion, including two settlements in the Second Circuit itself. Because settlements with pharmaceutical companies for off-label marketing have been so successful, there is little reason for the Department of Justice to abandon its tactic of aggressive prosecution.[179] Not only will government continue to prosecute off-label promotion and regard it as a per se violation of the misbranding provision, but pharmaceutical manufacturers are also not optimistic that the Second Circuit's decision will be a useful defense. Instead, pharmaceutical companies appear to prefer to settle and plead guilty.

The government decided not to bring the Second Circuit's decision to the Supreme Court for further review. It did not believe that the *Caronia* decision will impact the FDA's ability to

[179] *See* Vicki W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of Approved Drugs: Why the False Claims Act is the Wrong Rx*, 12 J. HEALTH CARE L. & POL'Y 119 (2013).

enforce the FDCA's drug misbranding provisions.[180] The likely reasons for the government's unwillingness to appeal the decision to the Supreme Court are two-fold. First, the Second Circuit's decision in *Caronia* did not question the validity of the misbranding provisions of the FDCA or find a conflict between these provisions and the First Amendment. Secondly, the Second Circuit did not strike down the FDCA's drug approval framework. Since the *Caronia* decision is only binding on courts with the Second Circuit, the government may not want to risk a broadly applicable decision by the Supreme Court—especially in light of the Supreme Court's decision in *Sorrell* which is protective of pharmaceutical speech.

Part VI: Conclusion

Although the *Caronia* decision was initially hailed as a "landmark" case and regarded as a victory for off-label and unapproved marketing, its impact has been limited. There is a circuit split on the issue of whether off-label drug promotion is prohibited under the misbranding provisions of the FDCA. Because the federal government has decided not to appeal the decision and bring it before the Supreme Court, circuits in the United States have the authority to decide the persuasiveness and applicability of the Second Circuit's decision. In addition, the large number of off-label promotion settlements with some of the nation's largest pharmaceutical manufacturers and distributors shows that *Caronia* did not impede the federal government's enforcement and prosecution of the misbranding provisions under the FDCA. Three settlements following *Caronia* fell within the jurisdiction of the Second Circuit, where the *Caronia* decision would be binding. Regardless, the three pharmaceutical companies pled guilty to misbranding their respective drugs and ultimately settled with the government.

[180] *See* Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J., (Jan. 23, 2009).

Although such a situation is unlikely given the case law and actions against pharmaceutical companies for off-label marketing since *United States v. Caronia*, if the FDA was hindered by the decision in *Caronia*, it still has an alternate avenue which to prosecute for off-label marketing. The federal government would be able to allege violations of the False Claims Act ("FCA") for off-label promotion. Under this alternative claim, the government could allege that a pharmaceutical company promoted the sale and use of drugs for uses that are not FDA-approved and not covered by the federal health care programs; thus, the promotion of off-label uses would result in the submission of false claims. Regardless of whether the government prosecutes off-label promotion under the Food, Drug and Cosmetic Act or under the False Claims Act, it is evident that a free speech defense is weak at best. The "side effect," or predicted results, of the *Caronia* decision have not been as desirable as anticipated.