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Off-Label Promotion After United States v. Caronia

Brian M. Blood*

Perhaps you’ve spotted them at your primary care physician’s office during your annual physical, or maybe you’ve simply heard anecdotes about them taking prescribers out to lavish meals. Maybe you’ve simply wondered where the stationary, pens, or other supplies bearing drug names at your physician’s office come from. Whatever your experience or opinion might be, you’re likely aware that drug and medical device manufacturers employ sales representatives to promote their products directly to physicians and other prescribers.¹ Despite a common preconception regarding the representative-prescriber relationship—that representatives utilize gifts and meals to unduly influence the prescriber into prescribing more of their company’s products²—the profession is highly regulated and representatives play an important role in patient treatment.³ Sales generated through representatives’ promotional activities ensure the profitability of a product, help to offset the manufacturer’s drug or device approval costs, and allow for continued research and development efforts.⁴ Further, representatives ensure that pertinent information regarding a certain product reaches prescribers, increasing the relevant information at the prescriber’s disposal and allowing for informed treatment decisions.⁵

Manufacturers face a lengthy and costly process in getting new prescription drugs and devices approved by the Food and Drug

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4. Id.

5. Id.
Administration (FDA)—FDA approval can take as long as twelve years and cost more than $500 million. Given the steep costs of getting a new drug to the market, manufacturers rarely seek approval for multiple or secondary treatment indications for a given product, despite any evidence of the secondary indication’s efficacy. Because of this deterrent to seeking secondary approval for a product, manufacturers largely rely on prescribers to prescribe a product for off-label uses that have not been specifically approved by the FDA and do not contain instructions for use on the product’s packaging or label. An estimated twenty-one percent of prescriptions nationwide are for off-label uses.


8. Rebecca Dresser & Joel Frader, Off-Label Prescribing: A Call for Heightened Professional and Government Oversight, 37 J.L. MED. & ETHICS 476, 476 (2009). While secondary approval would allow a manufacturer to engage in the full range of promotional activities related to a product’s additional use, manufacturers do not seek secondary approval for a number of reasons. Id. at 478. The secondary approval process, while not as costly or time-consuming as the initial process, still requires that, among other things, a manufacturer submit to the FDA additional data demonstrating the product’s effectiveness for the new use. See 21 C.F.R. § 314.70 (2008). In light of the costs associated with acquiring and submitting this new data, manufacturers might determine that the patient population for the secondary use is sufficiently small to deter secondary approval, or that profits from off-label prescribing are sufficiently high without seeking secondary approval. See Dresser & Frader at 476.

9. See Randall S. Stafford, Regulating Off-Label Drug Use – Rethinking the Role of the FDA, 358 NEW ENG. J. MED. 1427, 1427 (2008). Note that instructions or information regarding a product’s off-label indications are not included in the product’s labeling and packaging. Common examples of products used off-label include the drugs, by trade name, Elavil, approved for depression but also prescribed to prevent migraines, Topamax, approved for epilepsy but also prescribed for alcohol addiction, and Zyprexa, approved for schizophrenia and bipolar disorder but also prescribed for dementia. Luciana Gravotta, Why Doctors Prescribe Off-Label Drugs, SCIENTIFIC AMERICAN (Apr. 11, 2013), http://www.scientificamerican.com/article.cfm?id=why-doctors-prescribe-off-label-drugs.

10. David C. Radley, Stan N. Finkelstein & Randall S. Stafford, Off-Label Prescribing Among Office-Based Physicians, 166 ARCHIVES INTERNAL MED. 1021, 1021 (2006); see also Darshak Sanghavi, Cooking the Books: The Statistical Games
indicating that a significant portion of a manufacturer's revenues on product sales are through off-label prescribing.\textsuperscript{11} Further, for diseases affecting a very small portion of the population, the costs associated with FDA approval likely outweigh the possible revenue for the manufacturer, making off-label prescribing the patient's only treatment option.\textsuperscript{12}

Physicians are free to prescribe products to patients for reasons the physicians find medically appropriate, regardless of whether the indication is FDA-approved and listed on the manufacturer's product packaging and label.\textsuperscript{13} At the same time representatives, who conduct what is referred to broadly as "detailing,"\textsuperscript{14} are paid commissions based on the volume of specific drugs prescribed within their sales region; thus, they have an incentive to promote a drug for all indications.\textsuperscript{15} However, representatives are prohibited from marketing products for off-label


\textsuperscript{11} See, e.g., David Evans, \textit{Pfizer Broke the Law by Promoting Drugs for Unapproved Uses}, BLOOMBERG (Nov. 9, 2009, 12:01 AM), http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yY1nYxCGoA (indicating that Pfizer, which was fined for its off-label promotion of the drug Neurontin, made approximately $2.12 billion in 2002 alone on off-label prescriptions of the drug). \textit{See also} Radley et al., supra note 10, at 1021. It should also be noted that three-quarters of marketed prescription drugs have no labeling indications for children; thus, prescribing to a child will likely be considered off-label. Tracy Hampton, \textit{Experts Weigh in on Promotion, Prescription of Off-Label Drugs}, 297 J. AM. MED. Ass'n 683 (Feb. 21, 2007), http://jama.jamanetwork.com/article.aspx?articleid=205641.


\textsuperscript{13} See Dresser & Frader, \textit{supra} note 8, at 476.


indications, even if the marketing in question is a simple discussion with a prescriber about the non-fraudulent or truthful off-label use of a product.\textsuperscript{16} This prohibition comes in the form of government prosecutions against both the representative and the manufacturer for off-label promotion under either the Food and Drug Cosmetic Act’s (FDCA)\textsuperscript{17} misbranding provisions or the Federal False Claims Act (FCA).\textsuperscript{18} This Note focuses on the FDCA provisions.

The FDCA contains no express prohibition on off-label marketing by manufacturers and their representatives, but the government has interpreted the statute as prohibiting the activity.\textsuperscript{19} The consequences of off-label promotion—both fraudulent and truthful—can be detrimental for manufacturers. From 2004 to 2010, the government settled twenty-one cases involving off-label marketing, with over half of these settlements amounting to more than $100 million each.\textsuperscript{20} In 2009, for example, Pfizer paid a fine of $2.3 billion to the FDA for the off-label promotion of their drug Bextra.\textsuperscript{21} In addition, more than seventy percent of these cases have ended in criminal pleas.\textsuperscript{22}

In \textit{Sorrell v. IMS Health, Inc.},\textsuperscript{23} decided in June 2011, the Supreme Court of the United States addressed the practice of data mining, a subset of manufacturer detailing whereby pharmaceutical companies use data related to a particular physician’s prescribing

\begin{enumerate}
\item[16.] See 21 U.S.C. § 331(a), (b), (d) (2012) (prohibiting the misbranding of drugs and devices, which has been interpreted to include promoting such products off-label).
\item[18.] 31 U.S.C. § 3729 (2012). See Khan & Holloway, \textit{supra} note 3, at 410. Note that the FCA comes into play where government programs such as Medicare or Medicaid are billed for the allegedly fraudulent activity. 31 U.S.C. § 3729(a)(1)(A) (imposing liability on any person who presents or causes to present a false or fraudulent claim for payment or approval to one of the federal programs).
\item[21.] Gardiner Harris, \textit{Pfizer Pays $2.3 Billion to Settle Marketing Case}, N.Y. TIMES (Sept. 3, 2009), at B4.
\item[22.] See Giuliana, \textit{supra} note 20.
\item[23.] \textit{--} U.S. --, 131 S. Ct. 2653 (2011).
\end{enumerate}
practices to target marketing efforts at specific populations or individuals. The Court found that a Vermont law prohibiting pharmacies from selling data related to prescription patterns created both speaker- and content-based speech restrictions, and that, despite substantial government justification for the law, it was unconstitutionally restrictive of the company’s right to free speech.

Then, in December 2012, the Second Circuit Court of Appeals decided United States v. Caronia. The defendant in Caronia was a representative who was recorded telling a doctor that a medication approved for a narrow set of conditions could also be used to treat other conditions. The representative was prosecuted for violating the FDCA’s misbranding provisions. In its decision, the Second Circuit determined that prosecuting representatives’ truthful off-label speech under the FDCA violated the First Amendment. The Second Circuit held (1) that the government had prosecuted Caronia for his content- and speaker-based speech, (2) that the FDCA misbranding provisions and the government’s interpretation of the provisions were subject to heightened scrutiny, and (3) that truthful and non-fraudulent off-label drug promotion was speech protected by the First Amendment under both Sorrell and the four-prong test established by Central Hudson Gas & Electric Corp. v. Public Service Commission of New York. The Caronia decision prompted a wave of analysis, commentary, and prognostication for the future of off-label marketing.

24. The data at issue in Sorrell was “prescriber-identifying information” that pharmacies receive when processing prescriptions. Id. at 2659–2660.
25. See id at 2659.
26. See id. at 2662–65.
27. Id. at 2672.
28. 703 F.3d 149 (2d Cir. 2012).
29. Id. at 156.
30. Id. at 157.
31. Id. at 164.
33. Caronia, 703 F.3d at 164.
This Note proceeds in three Parts. Part I establishes the background of off-label regulation and interpretation, focusing on the FDCA provisions, government guidance, and the recent Supreme Court case Sorrell v. IMS Health, Inc. Part II details the 2012 Second Circuit case United States v. Caronia. Finally, Part III discusses the implications for the parties involved in the representative-prescriber relationship if the Caronia holding were to be applied beyond the Second Circuit, as is suggested by the Supreme Court's holding in Sorrell. Most notably, Part III.C discusses the implications of these holdings for the government and analyzes the alternatives to the current off-label regime suggested by the Caronia court.

I. FDA REGULATIONS AND SORRELL V. IMS HEALTH, INC.

The process of bringing a new drug or medical device into the market is both time-consuming and costly. A manufacturer must follow a strict process enacted by the FDA, including, but not limited to, conducting manufacturer-funded clinical trials for efficacy and safety for each intended use of the drug. The FDA approves drugs for a narrow set of conditions, not for universal use, and off-label marketing occurs when a manufacturer endorses a drug for uses that have not been

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35. See infra Part I.
36. 703 F.3d 149 (2012). See infra Part II.
38. See infra Part III.C.
41. See Stafford, supra note 9, at 1427.
approved by the FDA. Prescribers, however, can lawfully prescribe a drug for any indication that they feel is medically necessary, regardless of the scope of FDA approval and despite the strict regulations applicable to manufacturers.

The FDCA and its accompanying regulations set forth the requirements governing the manufacture and branding of pharmaceuticals, medical devices, and biological products. Specifically, the FDCA provides that a product’s labeling may only contain information on the product’s FDA-approved uses, and defines labeling narrowly to include the tangible materials that accompany a drug, such as packaging and product labels. The FDA, however, defines labeling as any materials or information that a manufacturer or its employees—including sales representatives—might produce, including their speech, regardless of whether the information accompanies the drug itself.

It is the FDA’s broad interpretation of labeling that the Justice Department utilizes in enforcing the FDCA’s misbranding provision, allowing the government to punish manufacturers that make assertions inconsistent with a product’s labeling. Thus, any statement about a product made by a manufacturer or representative is considered to be about the drug’s “intended use,” and the statement may only reference the FDA-approved uses of the product. Otherwise, the statement will qualify as misbranding or mislabeling, and the FDCA criminalizes the distribution or introduction of misbranded drugs into the stream of commerce. This expansive definition of labeling in the application of the FDCA’s misbranding provisions thus permits physicians to prescribe a product for any indication they feel is medically necessary while

42. Id.
43. Id.
46. See 21 U.S.C. §§ 321(p), 355(a), (b), (j).
47. See 21 U.S.C. §§ 321(p), 352(a), 355(a), (b), (j); see also 21 C.F.R. § 201.1-201.58 (2009).
restricting manufacturers and representatives in promoting a product, regardless of the assertions' truthfulness.  

The FDA has, however, established certain exceptions that allow manufacturers to promote a product for off-label uses. Prescriber knowledge of a product's effective off-label use is the only means by which a drug will be prescribed off-label. As such, manufacturers may, at the request of the prescriber, distribute the results of peer-reviewed studies appearing in publications with an expert editorial board. Several conditions attach, namely that the studies (1) should not be influenced by the manufacturer in any way and (2) must be distributed under strict FDA guidelines. The FDA also encourages manufacturers to seek amended secondary approval for additional "intended uses," which requires the manufacturer to reenter the FDA-approval process, though the secondary approval process is then less intensive.

As previously mentioned, the Supreme Court addressed the protection of commercial speech as it relates to a manufacturer's ability to solicit physician prescribing information and a pharmacy's ability to profit from prescription information in Sorrell v. IMS Health, Inc. The Sorrell Court found a 2007 Vermont law prohibiting such practices to be unconstitutional. In doing so, the Court held that both the

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50. See Iraggi, supra note 34, at 1144.
51. See, e.g., Stafford, supra note 9, at 1427–28.
52. The editorial board of the publishing organization must use "experts who have demonstrated expertise in the subject of the article under review by the organization . . . who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles," and the publication must have a publicly-stated conflict of interest policy requiring disclosure of any conflicts or biases among authors, contributors, or editors. U.S. DEP'T OF HEALTH AND HUMAN SERVICES, GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (Jan. 2009), available at http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf [hereinafter GUIDANCE FOR INDUSTRY].
53. See id.
54. Id.
56. Id. at 2659.
manufacturer’s right to market to physicians and the pharmacy’s right to sell prescription information are protected by the First Amendment.\(^5\)

The Sorrell Court used a two-step inquiry: first considering whether the speech-restricting regulation was content-based, forbidding particular content of the speech (i.e. marketing), and speaker-based, restricting the speech of a particular speaker (i.e. detailers),\(^5\) and then considering whether the government had adequately shown that the restrictions survived the applicable level of scrutiny.\(^5\)

The Court found that because the Vermont statute set forth both content-based restrictions on the marketing of prescriber information and speaker-based restrictions on manufacturers, the statute was subject to heightened scrutiny.\(^6\) The Court held that speech in aid of pharmaceutical marketing is a form of expression protected by the First Amendment,\(^6\) thus in the face of heightened scrutiny the Vermont regulation was presumptively invalid.\(^6\) Recognizing that the State was required to show “at least that the statute directly advance[d] a substantial governmental interest and that the measure [was] drawn to achieve that interest” without disproportionately burdening the speech,\(^6\) the Court noted Vermont’s stated interests of protecting medical privacy and achieving policy goals geared towards improved healthcare at lower costs.\(^6\)

In the second step of the Sorrell analysis, the Court applied the test espoused in Central Hudson Gas & Electric Corp. v. Public Service Commission of New York,\(^6\) determining that the Vermont statute failed even under the lesser standard of intermediate scrutiny.\(^6\) Central Hudson applied a four-part test and an intermediate level of scrutiny to determine

\(^{57}\). Id.
\(^{58}\). Id. at 2656–57.
\(^{59}\). Id. at 2663.
\(^{60}\). Id. at 2663–67.
\(^{61}\). Id. at 2667–68.
\(^{62}\). Id.
\(^{63}\). Id.
\(^{64}\). Id. at 2668.
\(^{65}\). 447 U.S. 557 (1980).
\(^{66}\). Sorrell, ___ U.S. at ___, 131 S. Ct. at 2667–68. In other words, the Sorrell Court, by adhering to the Central Hudson test, inserted a four-step test into its second prong instead of proposing a new five-step test encompassing all factors.
the constitutionality of a regulation restricting commercial speech. The first prong requires that the speech not be misleading and concern lawful activity. If the speech does not meet this requirement, it is afforded no First Amendment protection and can be reasonably regulated. The second and third prongs of the Central Hudson test require that the asserted government interest be substantial, and that the regulation directly and materially advance the asserted government interest. Finally, the fourth prong requires that the regulation be narrowly drawn and not be more extensive than necessary to serve the asserted government interest. The Sorrell Court decided that, even without applying the Central Hudson test, the Vermont law was both a content- and speaker-based regulation on its face, thereby triggering heightened scrutiny. Determining that the law did not meet the heightened scrutiny, the Court held that “[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment.” Further, in suggesting less restrictive alternatives and indicating that Vermont allowed for the information to be disseminated to all but a limited class of speakers, the Court determined that the statute was not narrowly tailored enough to the state’s interest to satisfy the heightened scrutiny.

The precedent established in Sorrell, whereby the Court utilized a two-step analysis encompassing the Central Hudson test to determine the validity of a law prohibiting manufacturer and representative speech, was recently applied by the Second Circuit in United States v. Caronia. Caronia directly addresses the FDCA’s misbranding provisions following the conviction of a representative for truthful off-label promotion.

68. Id. at 566.
69. Id.
70. Id.
71. Id.
72. See Iraggi, supra note 34, at 1148.
74. Id. at 2668–69.
75. 703 F.3d 149, 164 (2012).
76. Id. at 157–58.
II. UNITED STATES V. CARONIA

Alfred Caronia was a Specialty Sales Consultant employed by Orphan Medical, Inc.\textsuperscript{77} to promote Xyrem, a drug approved to treat narcoleptic patients with cataplexy and excessive daytime sleepiness.\textsuperscript{78} As required by the FDA, Xyrem has a “black box” warning, the most serious kind of warning required by the FDA to be placed on a product’s labeling and packaging.\textsuperscript{79} In a recorded conversation between Caronia and a prescriber, Caronia promoted Xyrem for off-label uses.\textsuperscript{80} Caronia was subsequently convicted of conspiracy to introduce a misbranded drug into interstate commerce in violation of the FDCA’s misbranding provisions, 18 U.S.C. § 371(a) and 21 U.S.C. § 331(a).\textsuperscript{81} On appeal, Caronia argued that his conviction should be overturned because he had been truthfully promoting the drug and had not misrepresented the safety or efficacy of Xyrem.\textsuperscript{82} The government contended that Caronia’s conviction did not implicate the First Amendment because he had not been punished for engaging in protected speech; rather, his statements had merely evinced the intent necessary to establish misbranding for a non-approved drug use.\textsuperscript{83}

In a 2-1 decision, the Second Circuit rejected the government’s assertion that the First Amendment did not apply, holding that the FDA and the government had improperly prosecuted Caronia for his off-label marketing of Xyrem.\textsuperscript{84} Applying the \textit{Sorrell} analysis, the court held that the First Amendment applied to the statements at issue because the FDCA provisions restrict both content- and speaker-based speech.\textsuperscript{85} Under the second prong of the \textit{Sorrell} analysis, the court applied the \textit{Central Hudson} test to determine whether the restrictions imposed on


\textsuperscript{78.} See Caronia, 703 F.3d at 155 (explaining that the active ingredient in Xyrem is gamma-hydroxybutyrate, also known as the “date rape drug”).

\textsuperscript{79.} \textit{Id.}

\textsuperscript{80.} \textit{Id.} at 158, n.6.

\textsuperscript{81.} \textit{Id.} at 159; see also 18 U.S.C. § 371(a) (2012); 21 U.S.C. § 331(a) (2012).

\textsuperscript{82.} Caronia, 703 F.3d at 160.

\textsuperscript{83.} \textit{Id.} at 160–61.

\textsuperscript{84.} \textit{Id.} at 152.

\textsuperscript{85.} \textit{Id.} at 164.
Caronia by the government’s interpretation of the FDCA could withstand heightened scrutiny. 86 The Second Circuit determined that the first two elements of the Central Hudson test were easily met. 87 As to the first element, the court found that because physicians and other prescribers may lawfully prescribe drugs for off-label indications, the speech at issue concerned lawful activity. 88 For the second element, the court determined that the government and the FDA had a substantial interest in “preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs.” 89

The court found, however, that the government could not satisfy the third and fourth prongs of the Central Hudson test. 90 Under the third prong, the court stated that off-label prescribing and usage is not unlawful and that the FDA’s product approval process contemplates that approved drugs will be used for off-label purposes. 91 Noting the government’s substantial interests, 92 the court nonetheless found that prohibiting truthful promotion of off-label use of a product by a certain class of speakers while allowing off-label prescribing by practitioners would not directly further the government’s goals. 93 Further, the court stated that the third prong failed because the law “‘paternalistically’ interferes with the ability of physicians and patients to receive potentially relevant treatment information” 94 by legalizing the outcome but prohibiting “the free flow of information that would inform that outcome.” 95

The Caronia court then determined that the government’s interpretation of the FDCA, which imposes a “complete and criminal ban on off-label promotion by pharmaceutical manufacturers,” fails the fourth prong of the Central Hudson test by being “more extensive than

86. Id. at 164–67. The court here, like in Sorrell, does not indicate exactly which level of scrutiny they are applying, but the Central Hudson test seems to be less onerous than strict scrutiny.
87. Id. at 165–66.
88. Id.
89. Id. at 166.
90. Id. at 166–68.
91. Id. at 166.
92. Id. at 166–67.
93. Id. at 166.
94. Id.
95. Id. at 167.
necessary to achieve the government’s substantial interests.”96 The court stated, “[W]e decline to adopt the government’s construction of the FDCA’s misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech.”97 Thus, in applying Sorrell and Central Hudson, the Caronia court found that off-label speech is protected by the First Amendment and that the government’s enforcement of off-label promotion under the FDCA unconstitutionally restricts a manufacturer’s free speech.98

In holding that the government’s interpretation of the FDCA off-label provisions fails the fourth step of the Central Hudson analysis, the court listed several “narrowly drawn” alternatives that it claimed would advance the integrity of the FDA’s drug approval process without creating excessive First Amendment restrictions.99 The court suggested that the government should more directly address the issue if it is concerned about the use of approved products for off-label purposes.100 Moreover, if the government has concerns with marketers misleading patients via off-label promotion, the court suggested “guid[ing] physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information.”101

The court next posited that the government could develop a warning or disclaimer system, or “safety tiers within the off-label market,” to distinguish drugs requiring extra caution.102 Alternatively, the court suggested, “the government could require manufacturers to list all applicable or intended indications” of a product when applying for FDA approval, enabling physicians, the government, and patients to track a drug’s development.103 Further, the court stated that in order to minimize off-label use or prevent evasion of the FDA approval process, the government could (1) create ceilings or caps on off-label prescriptions of a product, (2) remind the parties involved of the legal liability for off-

96. Id.
97. Id. at 168.
98. Id.
99. Id. at 167–68.
100. Id. at 168.
101. Id.
102. Id.
103. Id.
label promotion, or (3) prohibit off-label prescribing altogether for particularly dangerous products.104 Despite the government's argument that alternatives to the current FDCA provisions would not be administrable, feasible, or effective, the Caronia court determined that, in the absence of convincing evidence to the contrary, alternatives to the FDA's enforcement of non-fraudulent off-label speech would provide a better fit than the current system.105

The dissenter in Caronia argued that the majority undermined the fundamental purpose of the FDCA, which is to ensure the safety and efficacy of drugs through a rigorous premarket approval process.106 The dissent posited that, should manufacturers be permitted to lawfully market their products for off-label uses, their incentive to seek further approval would be eliminated, and the FDA's ability to determine all risks and benefits of a drug would be threatened.107 Further, the dissent accused the majority of incorrectly framing the FDCA's restriction on off-label promotion as a barrier to the ability of physicians to receive potentially relevant treatment information, and argued that the court's decision ran the risk of rendering the entirety of the FDCA unconstitutional.108

III. MANUFACTURER, PHYSICIAN, AND GOVERNMENT IMPLICATIONS

The repercussions of the Caronia decision have yet to be felt, and despite a wealth of scholarship on the decision since it was rendered,109 it is unclear whether Caronia will be viewed as a turning point in First Amendment jurisprudence related to off-label marketing or as an outlier from the Second Circuit.110 There are certainly cogent arguments, discussed by several commentators, that the FDA's regulatory program should not be treated the same as other content- and speaker-based restrictions due to off-label marketing's potential to pose

104. Id.
105. Id. at 168–69.
106. Id. at 177–78 (Livingston, J., dissenting).
107. Id. at 178.
108. Id. at 179.
109. See supra note 34.
110. See, e.g., Poulos & Rao, supra note 34, at 46.
significant risks to patients.\textsuperscript{111} Despite these arguments, the government, perhaps fearing that a loss at the Supreme Court would invalidate the FDA's entire approval and enforcement systems, chose not to seek certiorari.\textsuperscript{112}

The \textit{Caronia} holding itself is limited in a number of ways, the most obvious being that the case is binding only in the Second Circuit.\textsuperscript{113} Manufacturers operating within that jurisdiction, however, which encompasses Connecticut, New York, and Vermont, likely also distribute products outside of those states, and thus can still be subject to the FDA's current enforcement scheme.\textsuperscript{114} Further, the scope of \textit{Caronia} is narrow in that the decision only made a determination on the constitutionality of prosecutions under the FDCA's misbranding provisions and did not address enforcement of the FCA's off-label marketing provisions.\textsuperscript{115} The speech protected by the ruling is also limited to \textit{truthful} speech for off-label promotion of products for which off-label use is not prohibited,\textsuperscript{116} whereas the majority of recent government settlements in off-label cases have alleged fraudulent or

\textsuperscript{111}See Recent Cases, \textit{supra} note 34, at 799–800 (describing the adverse regulatory and public health effects that applying a more demanding commercial speech inquiry to prescription drug regulations would create); \textit{see also} Ralph S. Tyler et al., \textit{Anomalies and Implications: The First Amendment and "Off-Label" Promotion, FOR THE DEFENSE}, Oct. 2012, at 34, 38 (illustrating the unique regulatory approach for off-label promotion, whereby the government willingly pays for medically-appropriate off-label products via Medicare and Medicaid while the Department of Justice punishes manufacturers for promoting those same products for off-label use).


\textsuperscript{113}See Caronia, 703 F.3d at 149.

\textsuperscript{114}See Scheineson & Cuevas, \textit{supra} note 34, at 214.

\textsuperscript{115}See Iraggi, \textit{supra} note 34, at 1155–56 (pointing out that \textit{Caronia} is significant because it: (1) relied heavily on \textit{Sorell} in the determination that the FDCA provisions represented content- and speaker-based restrictions; (2) disregarded a strict scrutiny standard, although available, and instead applied the less strict \textit{Central Hudson} test; and (3) that the scope was narrowed by not addressing FCA claims).

\textsuperscript{116}There might be instances where the off-label use is contraindicated. \textit{See} Poulos & Rao, \textit{supra} note 34, at 46.
misleading statements.\textsuperscript{117} Despite these limitations, \textit{Caronia} has been cited in a number of state and federal court cases and briefs, both within and outside of the Second Circuit’s jurisdiction, as establishing heightened scrutiny for content- and speaker-based restrictions related to off-label drug promotion.\textsuperscript{118}

The remainder of this Note assumes, for the sake of argument, that the \textit{Caronia} holding, which applies the \textit{Sorell} and \textit{Central Hudson} tests to the FDA’s enforcement of the FDCA’s off-label drug and device marketing restrictions, will be accepted by the Supreme Court. Under this assumption, the repercussions of \textit{Caronia} on manufacturers, physicians, and the government can be more readily assessed and the alternatives to the current FDA regime can be better analyzed. In the following subsections, the impact of the \textit{Caronia} holding will be analyzed in relation to (1) manufacturers, (2) physicians and patients, and (3) the government.

\textbf{A. Manufacturers}

Should the holding in \textit{Caronia}—that off-label promotion by representatives is constitutionally protected\textsuperscript{119}—be adopted by the Supreme Court and therefore apply nationwide, the result would be viewed as a coup for drug and device manufacturers. The holding would, in theory and in lieu of an alternative regulation scheme, free manufacturers and their representatives from liability for truthful off-label promotion and marketing. Therefore, many of the implications for manufacturers in terms of compliance and mitigation efforts post-\textit{Caronia} would largely depend on the government’s reaction and

\begin{itemize}
  \item \textsuperscript{117} \textit{Id.} (listing several recent settlements from the likes of GlaxoSmithKline and Pfizer alleging misleading fraudulent off-label marketing resulting in settlements in the tens of millions of dollars or more).
  \item \textsuperscript{119} United States v. Caronia, 703 F.3d 149, 149 (2d Cir. 2012).
\end{itemize}
If truthful off-label marketing is constitutionally protected, manufacturers might view the stated interest in *Caronia* (providing a flow of information to physicians and patients) as encouragement for promoting off-label indications in print advertisements, television commercials, or other direct-to-consumer advertising. The result from increased direct-to-consumer advertising would likely manifest in patients requesting specific prescriptions from their physicians, and the risk in such a scenario is that physicians might lack adequate information about the products being requested. Direct-to-consumer advertising, however, is independently and strictly regulated. Thus, without a judicial attack on the specific regulatory and enforcement schemes of direct-to-consumer advertising, the *Caronia* decision would have little conceivable affect on a manufacturer or representative’s ability to reach consumers directly, and would only affect interactions between representatives and prescribers.

*Caronia* might also change the landscape of the FDA approval process for manufacturers. The dissent in *Caronia* argued (and some commentators agree) that the impact of allowing manufacturers to make potentially unlimited claims of a drug’s non-approved indications would be drastic and would create a disincentive for alternate FDA approval. Under the current system, manufacturers are encouraged to have products approved for secondary indications through the FDA’s supplemental NDA approval process, which requires a showing by the manufacturer that the additional indications are supported by proof of the indication’s claims of benefit. If the FDA can no longer stop claims

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120. *Id.* at 166.
124. *See id.*
125. *See* Tyler et al., *supra* note 111, at 38.
126. *See* United States v. Caronia, 703 F.3d 149, 179 (2d Cir. 2012); *Yan, supra* note 34, at 192.
from being made without proof, misinformed treatment decisions might result from reduced supplemental NDAs and an “unreliable set of product benefit assertions.” Thus, as the Caronia dissent argues, manufacturers would lose any incentive to have their products approved by the FDA through legitimate, though burdensome and cost-prohibitive, means, instead relying on off-label promotion and marketing for unapproved product uses.

Additionally, the Caronia decision might drastically change the FDA’s ability to restrict non-oral communication regarding off-label use of products. Currently, the FDA allows manufacturers to provide a prescriber with available literature and scholarly articles regarding a product’s off-label use when the prescriber inquires as to the off-label use of a certain product either to a representative or directly to the manufacturer. The FDA’s Good Reprint Practice Guidance indicates that all written communication discussing off-label uses of a product should note that the off-label uses described have not been FDA approved. Further, the communication should (1) disclose any manufacturer financial interests in the studies cited, (2) include all significant risks and safety concerns known to the manufacturer, (3) be accompanied by approved product labeling, and (4) include a comprehensive bibliography of contrary authority. Following the Caronia decision, manufacturers might have less incentive to make these documents available to prescribers since representatives could directly communicate with the prescriber about truthful off-label indications.

128. Caronia, 703 F.3d at 179.
129. See generally Khan & Holloway, supra note 3, at 417–18 (describing the current restrictions on non-oral communications between manufacturers and prescribers).
130. GUIDANCE FOR INDUSTRY, supra note 52.
131. Id.
132. Id.
133. Id.
With less demand for scholarly, non-biased articles about a product’s off-label uses, the Caronia decision might distort the notion of truthful off-label promotion to the extent that a product’s off-label efficacy and safety are underreported or undetermined, yet still considered truthful and non-fraudulent. Despite the disincentive for manufacturers to provide adequate articles and research in this scenario, prescribers would likely not rely solely on a representative’s assertions, and would most likely still want to review documentation of a product’s off-label use before prescribing the product for such use.

B. Physicians and Patients

The majority opinion in Caronia stresses the importance of the relationship between doctors and patients, namely the role that prescribers play as gatekeepers between patients and potentially helpful treatments. Just as the government has an interest in protecting patients from unsafe and ineffective drugs, physicians have an interest in providing patients with treatment options that provide the best outcomes with the least chance of adverse effects.

Post-Caronia, prescribers and their patients would still be protected from fraudulent or untrue statements about a product’s off-label use via the government’s continued authority to punish fraudulent speech, as the decision renders only truthful speech constitutionally protected. Should the decision in Caronia apply nationwide, however, the interactions between representatives and prescribers would no longer be strictly limited to on-label and FDA-approved indications for a product. In this sense, Caronia potentially opens the flood gates for representatives attempting to market their company’s product’s off-label uses, and runs the risk of discouraging the flow of information related to on-label and FDA-approved product usages. Physicians generally have

136. United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012).
137. See, e.g., Khan & Holloway, supra note 3, at 408.
138. Id.
139. See, e.g., Recent Cases, supra note 34, at 802.
very little time to discuss products with representatives. 140 Thus, depending on the representative and the products being marketed, meetings between representatives and prescribers could potentially be focused on off-label uses for products rather than on soliciting and providing information related to FDA-approved uses. 141 By focusing on the stated purpose—encouraging the flow of information to physicians and patients—the decision could create a bottle-neck of information, with representatives presented with an incentive only to discuss the more lucrative product usages, whether on- or off-label.

The decision also might lead to discrepancy over what constitutes “truthful” speech in the context of representative-prescriber discussions. 142 Under the current regulatory scheme, representatives may not discuss off-label use of a product directly with a physician under any circumstances. 143 “Truthful” off-label information must be requested specifically by the physician and must be supplied in the form of peer-reviewed studies appearing in publications that meet various criteria. 144 If the Caronia holding is applied nationwide, physicians would presumably no longer have to request materials from a manufacturer’s marketing or compliance departments. Rather, physicians could discuss truthful off-label use directly with the representative, leaving open the possibility that “truthful” information will broaden in these interactions. 145 In lieu of a different regulatory approach by the FDA, it is unclear where the limit of truthful off-label speech would lie. 146 The FDA established the requirement that off-label information come in the form of peer-reviewed and edited publications to ensure that physicians receive information free from the taint of bias or inaccuracy. 147 If representatives can speak on behalf of the manufacturer, representatives may paint an accurate picture of an off-label study but fail to include sufficient information about

141. See id.
142. See Scheineson & Cuevas, supra note 34, at 215.
143. GUIDANCE FOR INDUSTRY, supra note 52.
144. Id.
146. See id.
147. GUIDANCE FOR INDUSTRY, supra note 52.
contraindications, side-effects, or information for minimizing the risks presented in the study.\textsuperscript{148}

Further, the decision might allow representatives to discuss findings disseminated from sources beyond the peer-reviewed scholarly articles currently allowed.\textsuperscript{149} In such a scenario, physicians, or the government in the case of a prosecution, may find it difficult to determine whether a representative’s claims are indeed truthful. In order to be protected by the First Amendment, commercial speech must both concern a lawful activity and not be misleading.\textsuperscript{150} In one sense, all off-label promotion is misleading because the statements have not passed the FDA-approval process and are not listed on the label.\textsuperscript{151} But even if truthful off-label promotion is constitutionally protected, the problems inherent in allowing representatives to discuss a limited amount of truthful off-label uses are apparent. What information representatives could discuss with prescribers, and the form of that information, would remain unclear,\textsuperscript{152} and without either an alternative regulatory scheme or a shift in the focus of off-label enforcement, the holding in \textit{Caronia} could threaten the flow of information that the majority so strongly emphasized.\textsuperscript{153}

\textbf{C. The Government}

The implications discussed thus far depend greatly on the government’s response to a situation where \textit{Caronia} is accepted nationwide. If the holding in \textit{Caronia} is adopted by the Supreme Court, one thing is for certain: the FDA will still regulate off-label promotion by

\textsuperscript{148} See Scheineson & Cuevas, supra note 34, at 215.

\textsuperscript{149} But see Khan & Holloway, supra note 3, at 430–31 (suggesting a safe harbor for speech related to off-label studies conducted via comparative effective research).

\textsuperscript{150} Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm’n of N.Y., 447 U.S. 557, 563, 566 (1980) (defining misleading speech as “communication more likely to deceive the public than inform it”).

\textsuperscript{151} See Polubinski, supra note 134, at 1025.

\textsuperscript{152} It is hard to imagine, for instance, a representative citing a scholarly article on a product’s off-label use with the level of technical specificity and lack of bias as would be present in the scholarly article.

\textsuperscript{153} United States v. Caronia, 703 F.3d 149, 167 (2d Cir. 2012).
representatives. This regulation could be in the form of a new regulatory scheme, a new definition of the FDCA provisions, or an enhanced focus on certain types of off-label promotion, separately or combined with other regulations.

Statements from the FDA following the decision have indicated that Caronia will not significantly affect the agency’s enforcement of the drug misbranding provisions of the FDCA, and point to the fact that enforcement based on false or misleading statements will continue unabated. Indeed, recent cases illustrate that prosecutions for fraudulent off-label marketing have continued to be pursued under both the FDCA and the FCA. For example, in March 2013, Par Pharmaceuticals pled guilty to a criminal misdemeanor for misbranding Megace ES in violation of the FDCA, agreeing to pay $45 million and enter into a five-year Corporate Integrity Agreement. Par had promoted Megace for use in elderly patients, an off-label use, despite never having conducted clinical studies on elderly people, and had allegedly made false and misleading claims about the efficacy of their product compared to rivals. Similarly, in United States v. Harkonen,

154. See, e.g., Khan & Holloway, supra note 3, at 414–16 (discussing FCA enforcement of fraudulent off-label promotion).  
157. See Press Release, supra note 156. A corporate integrity agreement for a health care provider is negotiated with the Office of Inspector General (OIG) as part of a settlement, and generally requires that the company institute or promote compliance measures such as hiring a compliance officer or appointing a compliance committee, developing written standards and policies, implementing training programs, and providing annual reports to the OIG. See Corporate Integrity Agreement, U.S. Dep’t of Health & Hum. Servs.: Office of Inspector General, https://oig.hhs.gov/compliance/corporate-integrity-agreements/index.asp (last visited Mar. 19, 2014).  
158. See Press Release, supra note 156.  
159. See Memorandum, U.S. v. Harkonen, supra note 156.
the Ninth Circuit upheld the conviction of the former CEO of InterMune, Inc. for wire fraud based on a press release allegedly containing false and misleading statements about the off-label use of a product. The court found that the statement was not "a scientific view" but was fraudulent and thus not protected by the First Amendment.

These cases illustrate that an emphasis on enforcement of fraudulent and misleading off-label speech has begun to occur. Focusing on fraudulent and misleading off-label speech leaves less room for future First Amendment challenges. Proving fraudulent speech also heightens the government's evidentiary burden by requiring the government to find and prove instances of fraudulent or false speech. Indeed, the government might even stop forbidding the "promotion" of off-label uses and start prohibiting altogether the introduction of drugs that the company intends to be used off-label. With these cases in mind, commentators have suggested that manufacturers should not alter their compliance efforts despite the victory in Caronia.

If the holding in Caronia were to be applied nationwide, however, the FDA would have to overhaul its enforcement of off-label promotion by manufacturers and their representatives. As discussed above, the Caronia majority held that a representative's truthful speech regarding off-label indications of a product is protected by the First Amendment, necessitating heightened scrutiny, and that the FDA's interpretation of the FDCA's provisions failed the third and fourth prongs of the Central Hudson test. Those prongs of the analysis

160. Id.
161. Id.
163. Id.
164. See id.
167. See Tyler et al., supra note 111, at 38.
168. See supra Part III.
specifically require that the law restricting protected speech both directly advance the government’s interest and be narrowly drawn to further the interest served. Thus, any alternative regulatory enforcement scheme would have to more directly advance the government’s interest in “preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs,” while not “interfer[ing] with the ability of physicians and patients to receive potentially relevant treatment information.”

Any alternative regulatory scheme proposed by the government would thus have to be more narrowly drawn than the current regime to further their interests. In looking at the Central Hudson test’s fourth prong, the court in Caronia makes several suggestions for government enforcement of off-label marketing that it felt would be more narrowly-tailored than the current system. These are obviously only suggestions for a more narrowly-drawn regulatory system, and a number of the suggestions in tandem might adequately advance the government’s interests while being better tailored to those interests.

1. Provide Guidance to Physicians

The first alternative the Caronia court suggests is aimed at the government’s interest in protecting physicians from off-label information that might be misleading. The opinion simply states that the government could “guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful and non-misleading information.” While it seems unlikely that this option would (or could) be enacted as a sole replacement for the current system, the suggestion taken on its own is insufficient for a number of reasons.

170. Id. at 166.
171. See id. at 167–68.
172. Id.
173. See Tyler et al., supra note 111, at 38.
174. Caronia, 703 F.3d at 168.
175. Id.
The *Caronia* majority does not go into any further detail than the language quoted above, and, as previously mentioned, the government's ability to prosecute fraudulent and untruthful off-label marketing does not change under the *Caronia* holding. Thus, even if the holding is accepted nationwide, it would still be unlawful under the FDCA and FCA for a manufacturer or representative to fraudulently market a product. The court's first suggestion, however, seems to presume either that the government would not continue to prosecute false or fraudulent statements under the FDCA misbranding and mislabeling provisions, or that enforcement would decrease to the extent that incentives for manufacturers and representatives to fraudulently market would increase. In either case, the opinion suggests that without the current program there would be enough fraudulent and false marketing conducted, and enough confusion on the part of prescribers, to necessitate government guidance in the first place.

It is also unclear what type of guidance the court is suggesting. Off-label indications by their nature presume a lack of government expertise and knowledge because they are outside FDA approval. On the one hand, the government could circulate or make more readily available the types of studies that manufacturers can provide to physicians under the current system. The government might also provide a "safe harbor" for drug companies to more liberally promote such studies to prescribers, and there is no question that increasing circulation of such items would bolster the flow of truthful information from manufacturer to prescriber.

It is unclear, however, whether the court is advocating an active step for the government that would require the spreading of truthful information about off-label prescription use as well as the collection and analysis of such information. Considering that off-label uses of a...
product are not the focus of the FDA during the approval process, an active step would require the government to, at the very least, disseminate peer-reviewed studies on the safe and effective off-label uses of a given product. At most, the government might fund the studies or conduct something akin to secondary approval for a drug product before suggesting (via dissemination of the articles) that certain off-label uses are safe and effective.\footnote{Khan & Holloway, supra note 3, at 430–31 ("[I]n the presence of research criteria that can be validated as trustworthy, the FDA should allow for wider and less restricted dissemination of off-label study findings.")}

The \textit{Caronia} court's suggestion also seems to ignore the manufacturer and representative side of the equation. It seems to presume that manufacturers and representatives will react to the \textit{Caronia} decision by increasing the volume and frequency of fraudulent off-label statements to the point that physicians would need guidance to sift through the product claims. If, on the other hand, manufacturers were given government assistance in the creation and dissemination of information regarding a product's off-label use, it is likely that such assistance would be effective in encouraging open channels of communication regarding effective off-label treatments.\footnote{John Osborn, \textit{Feds Have Beaten Pharma Into Submission Over Off-Label Drug Use, But at What Cost?}, FORBES PHARMA & HEALTHCARE BLOG (Nov. 7, 2013, 1:10 PM), http://www.forbes.com/sites/johnosborni/2013/11/07/hohum-another-multi-billion-dollar-drug-company-fraud-settlement/ ("[I]f the FDA

2. Provide Reminders as to Liability

Along the same lines, and perhaps suggested in concert with government "guidance," the court next suggests that "the FDA could further remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions."\footnote{Caronia, 703 F.3d at 168.} This suggestion seems to encompass two very different actions by the government. On one hand, whether manufacturers need to be reminded of liability regarding off-label prescribing is questionable considering the seemingly constant threat of enforcement for off-label promotion.\footnote{Caronia, 703 F.3d at 168.} Reminding physicians of liability related to medical
malpractice or negligence theories of liability would not hurt the parties involved. As with the manufacturers, however, a reminder of the threat of actions for such liability would, in all likelihood, render a reminder unnecessary.\textsuperscript{188}

On the other hand, the court suggests further regulating legal liability related to off-label promotion and treatments.\textsuperscript{189} Enacting regulations addressing the legal liability for manufacturer promotion or prescriber prescriptions of off-label products are certainly alternatives to the current system, but the \textit{Caronia} court offers no further indication of how these alternatives would address the government's interests better than the current system. Placing incentives on either the manufacturer or prescriber to ensure the safe prescribing of products for off-label use would be beneficial to overall patient safety, but increasing liability on either party for off-label treatment decisions, particularly if the decisions are based on an effective or truthful off-label use, would interfere with a prescriber's medical judgment.\textsuperscript{190} Further, if manufacturers are held liable for off-label treatment, they would essentially be responsible for something that they have very little control over, and such regulation would place an unfair burden on the manufacturer to monitor prescribing practices in order to ensure that physicians are prescribing the manufacturer's products correctly.

3. Develop Warning or Disclaimer Systems or Safety Tiers

While the \textit{Caronia} court's suggestions that the government provide further "guidance" and "regulation"\textsuperscript{191} are vague and would potentially be either ineffective if enacted alone or difficult to implement, the remaining suggestions are slightly more compelling.\textsuperscript{192} The opinion states that the government could "develop its warning or

\textsuperscript{188.} \textit{Id.}

\textsuperscript{189.} \textit{See} Osborn, \textit{supra} note 48, at 306–07 (describing the "vigorous policy debate over the significance and validity of truthful medical and scientific information that is not included in the FDA-approved label").

\textsuperscript{190.} \textit{Id.} at 303–04.

\textsuperscript{191.} \textit{Caronia}, 703 F.3d at 168.

\textsuperscript{192.} \textit{Id.}
disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs.\textsuperscript{193} The court cites to an article in which the author argues that manufacturers should be permitted to provide information about off-label use to physicians as long as the information provided is accompanied by an adequate disclaimer regarding the scientific bases of the off-label use.\textsuperscript{194}

Providing a disclaimer regarding the bases of peer-reviewed studies of off-label uses would, in theory, further inform prescribers of the potential risks of a product’s off-label use, but runs the same risk of untruthfulness that any other manufacturer communication runs, and the disclaimers would have to be closely monitored. Furthermore, product labels already contain information about potential side-effects and contraindications, thus additional warning would add little marginal value.\textsuperscript{195} The product at issue in Caronia, in fact, was required by the FDA to be accompanied by a “black box” warning, which is “the most serious warning placed on prescription medication labels,” and warned against safety and efficacy in certain patients.\textsuperscript{196} Additionally, the FDA regulates the distribution of the drug at issue in Caronia by allowing only one centralized pharmacy to distribute the product nationwide,\textsuperscript{197} suggesting that the safety of the drug should be obvious to prescribers. If the FDA wanted to completely prohibit the off-label prescribing of a certain product, as the Caronia opinion later suggests,\textsuperscript{198} they likely could.\textsuperscript{199}

Providing safety tiers or further warning systems for off-label use is slightly problematic, namely because information regarding a product’s off-label use, by nature of being “off-label,” is not included on

\begin{itemize}
\item \textsuperscript{193} Id. (citing Coleen Klasmeier & Martin H. Redish, \textit{Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech and Protection}, 37 AM. J. L. & MED. 315, 334 (2011)).
\item \textsuperscript{195} See id.
\item \textsuperscript{196} Caronia, 703 F.3d at 155.
\item \textsuperscript{197} Id.
\item \textsuperscript{198} Id. at 168 (“[W]here off-label drug use is exceptionally concerning, the government could prohibit the off-label use altogether.”).
\item \textsuperscript{199} Id. at 168.
\end{itemize}
the product’s labeling or in the product’s packaging. One of the
dangers of off-label treatments is surely the risk of incorrect or
dangerous dosages in the absence of FDA-approved indications, but
providing further directions beyond the findings and indications of peer-
reviewed studies would require an additional step towards legitimizing
the practice of off-label prescribing. This additional step might further
incentivize manufacturers to avoid supplemental approval for a
product. It is also unclear what warning system the court is suggesting
beyond the current “black box” and distribution restrictions already
available to the FDA.

4. Require a List of All Intended Indications During the Initial Approval
Process

The Caronia decision goes on to state that “the government
could require pharmaceutical manufacturers to list all applicable or
intended indications when they first apply for FDA approval, enabling
physicians, the government, and patients to track a drug’s development.” This suggestion assumes that a product will be
prescribed off-label for all intended indications a manufacturer is aware
of prior to FDA-approval, regardless of the indication’s efficacy, and that
a manufacturer will be aware of all possible off-label indications when
submitting a product to the FDA for approval. It would thus open the
possibility that a manufacturer could list a wide range of “possible”
intended indications prior to the FDA approval process in the hopes that
the product, after being approved for limited uses, could be prescribed
for a variety of indications. When the FDA approves a product in this
scenario, there is a risk that information distinguishing safe from
effective off-label uses from ineffective uses would not be readily
available.

200. See Recent Cases, supra note 34, at 800–02.
201. Khan & Holloway, supra note 3, at 428.
202. Id.
203. See Caronia, 703 F.3d at 155.
204. Id. at 168.
205. See, e.g., A. Elizabeth Blackwell & James M. Beck, Drug Manufacturers’
First Amendment Right to Advertise and Promote Their Products for Off-Label Use:
It is also questionable how closely and to what extent physicians or patients would actually track the progress of a product’s approval, particularly if the product in question will not be approved for the particular course of treatment. To the extent that such tracking would improve knowledge or awareness of a product’s safe and effective use, however, this tracking could benefit patients and further the government’s interests.

5. Create a Ceiling on Off-Label Prescriptions

Finally, and perhaps most persuasively, the Caronia opinion suggests that the government create “ceilings or caps on off-label prescriptions.” While placing a limit on the overall total of off-label prescriptions for drugs might negatively affect patients being treated with off-label products, commentators have suggested that a quota system, whereby a manufacturer is required to seek FDA-approval after off-label prescriptions of a particular product reach a certain number or percentage, would provide a speech-neutral alternative to the current system. By tracking off-label prescriptions via something similar to the Prescription Drug Monitoring Programs (PDMPs) that are currently active in forty-one states, the FDA could require that manufacturers submit a product for secondary approval once a certain threshold of prescriptions is met. This would allow manufacturers to truthfully market products for off-label use while ensuring FDA-approval of the product once prescriptions of the product reach a threshold limit.

Such a program would be difficult to enact, however, as there is currently no uniformity among the state PDMP programs, and the government would be required to pass legislation implementing such a program on a national scale in order to track all prescriptions written

206. Caronia, 703 F.3d at 168.
207. See Blackwell & Beck, supra note 205, at 460–61.
208. Iraggi, supra note 34, at 1160.
210. See id. at 1161–62.
211. Id. at 1160–62.
nationwide. The implementation and standardization of a national PDMP program would thus be costly and likely take great effort. Additionally, all prescribers would have to standardize their prescription pads or be compelled to write prescriptions via an electronic system so that their prescribing practices could be tracked. This would undoubtedly frustrate members of the medical community, whose discretion and medical judgment is a key interest at stake in such matters.

Manufacturers would likely also dislike being forced to seek FDA-approval simply because a product is successful for off-label use. Whereas under the current system manufacturers can seek secondary approval if they desire to lawfully promote a product, under the proposed quota system they would be compelled to file for such approval. The FDA could, potentially, make it easier for a successful off-label product to obtain secondary approval, but the process would still likely be costly and time-intensive. Drawbacks aside, limiting off-label prescriptions via a quota system would have the best chance of preserving the integrity of the FDA’s drug-approval regime, would most adequately replace the current enforcement regime for truthful off-label promotion and prescribing, and would allow for the free-flow of information between manufacturer and physician.

IV. CONCLUSION

It is too early to tell what effect, if any, the Second Circuit’s Caronia decision will have on the government’s regulation of off-label marketing by drug and device manufacturers and their representatives. Without knowing the government’s reaction, the implications for the other parties involved are unclear. The decision will likely have little effect outside of the Second Circuit for now, but the current system, whereby off-label promotion is illegal while off-label prescribing is permitted, does not adequately address the interests of the parties involved. In light of the Supreme Court’s holding in Sorrell, there is

212. Id.
213. See id.
214. Id.
215. Id.
216. Id.
217. ___ U.S. ___, 131 S. Ct. 2653.
hope that, should the Supreme Court hear a case similar to Caronia, it might find along the same lines as the Caronia court. On the other hand, there is also the possibility that the Supreme Court would find that the government's current interpretation of the FDCA satisfies heightened scrutiny and is the most narrowly-tailored option available. Until such an opinion occurs, however, manufacturers are stuck complying with regulations that criminalize the promotion of a legal activity.