The Sedona Conference Journal

Volume 14 2013

The Future of Off-Label Promotion Enforcement in the Wake of *Caronia*—Toward a First Amendment Safe Harbor

John C. Richter and Daniel C. Sale

Recommended Citation: John C. Richter & Daniel C. Sale, *The Future of Off-Label Promotion Enforcement in the Wake of Caronia—Toward a First Amendment Safe Harbor*, 14 SEDONA CONF. J. 19 (2013).

THE FUTURE OF OFF-LABEL PROMOTION ENFORCEMENT IN THE WAKE OF *CARONIA* – TOWARD A FIRST AMENDMENT SAFE HARBOR

*John C. Richter and Daniel C. Sale**
King & Spalding LLP
Washington, DC

On December 10, 1862, a paper reported that William Hammond, the Surgeon General of the United States Army, traveled from Washington, D.C. to Philadelphia, Pennsylvania to "investigate alleged frauds in the [Army's] Medical Purveying Department."[1] After "suspecting from strong evidence that all was not right there," the Surgeon General dispatched a medical inspector to make further inquiries into this case of health care contracting fraud.[2] Nearly one hundred and fifty years later, the United States Department of Justice issued a press release touting the fact that in fiscal year 2012, it recovered nearly $5 billion under the Civil War-era False Claims Act, of which recoveries for health care fraud amounted to over $3 billion.[3] While the government's tactics and focus have changed over the past century and a half, one thing is clear: health care fraud perpetrated against the government has been, and will continue to be, a prime law enforcement concern.

One particular concern in this area in recent years is fraud stemming from the off-label promotion.[4] In fact, the largest False Claims Act recoveries have all been off-label promotion cases.[5] It may come as a surprise to some then that the off-label *use* of drugs is perfectly legitimate, and that in certain circumstances the FDA has recognized that the off-label use of drugs may actually constitute the accepted medical standard of care.[6] Moreover, the term "off-label promotion" appears nowhere in the relevant statutory and regulatory text. Furthermore, notwithstanding aggressive enforcement in this area for many years, there remains minimal guidance and unclear statutes and regulations, which makes it challenging for drug manufacturers as they grapple with the government's expanding theories of liability for off-label promotion.[7]

---

* Mr. Richter is a litigation partner at King & Spalding LLP, where he specializes in representing companies and individuals facing government scrutiny. Mr. Sale is an associate at King & Spalding LLP, who likewise focuses on the representation of companies and individuals in white collar and government investigation-related matters.

1 *Frauds in the Medical Department*, N.Y. TIMES, Dec. 10, 1862, *available at* http://www.nytimes.com/1862/12/10/news/washington-important-matters-under-discussion-congress-question-arbitrary.html.

2 *Id.*

3 *See* DOJ Press Release, United States Department of Justice, Justice Department Recovers Nearly $5 Billion in False Claims Act Cases in Fiscal Year 2012 (Dec. 4, 2012), *available at* http://www.justice.gov/opa/pr/2012/December/12-ag-1439.html.

4 For the sake of clarity, the remainder of this Article will focus on the regulation of pharmaceutical drugs, and not medical devices. However, although the statutory citations may differ, the following discussion is generally applicable equally to medical devices.

5 *See Supra*, note 3.

6 *See, e.g.*, John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y, L. & Ethics 299, 303-04 (2010); James E. Beck and Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking the Myths and Misconceptions*, 53 Food & Drug Law. J. 71, 80 (1998) (estimating that off-label uses account for between 25 to 60 percent of all prescriptions written each year); *see also* Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694 (Jan. 13, 2009) (hereinafter, "Good Reprint Practices").

7 *See id.* at n.21 and accompanying text.

In the past, many off-label investigations focused on statements made, or materials disseminated by, manufacturers' sales representatives. Recent trends in off-label enforcement, however, show that the government is branching out from a purely sales and marketing focus and is now peeking under the hood of activities that were not, until recently, heavily scrutinized. The Food and Drug Administration ("FDA") and the Department of Justice ("DOJ") are now focusing on areas that historically have not generally been considered "promotional" in nature, including post-market clinical study design and conduct, the use (and misuse) of clinical data by manufacturers, and the use of continuing medical education programs and activities.

Recent cases, settlements, and enforcement actions illustrate this new focus for government in off-label promotion enforcement. This Article will analyze these actions. In recent years, manufacturers, their counsel, and other interested parties, have maintained that truthful off-label promotional speech is protected by the First Amendment of the United States Constitution.[8] While First Amendment challenges to the government's position on off-label promotion have not, generally, been well received by prosecutors,[9] manufacturers have been able to advance the argument over the years – notwithstanding the relative paucity of judicial review in cases of corporate prosecution.[10] Late last year, the United States Court of Appeals for the Second Circuit issued its decision in *United States v. Caronia*, holding that the government cannot prosecute pharmaceutical manufacturers and their representatives for speech promoting the lawful, off-label use of an FDA-approved drug.[11] While much ink has been spilled in the wake of the *Caronia* decision, it is already clear that the decision will not stop the government's enforcement focus on off-label promotion.[12] It will, however, force the government to focus on the truth or falsity of the alleged off-label promotional speech. In other words, the truthfulness of promotional speech will be a central issue in any off-label investigation, and the recent trend towards scrutiny of clinical data and the scientific exchange of information will become *de rigueur*.

This article will first provide a brief overview of the government's regulation of off-label medical and scientific information. Second, it will discuss the trend towards scrutiny of clinical data and the scientific exchange process. Third, the Article will discuss the intersection of the First Amendment and off-label promotion, and will highlight the *Caronia* decision. Fourth, with the First Amendment and *Caronia* cases as backdrop, this Article will analyze the implications of the *Caronia* decision, the current state of off-label promotion enforcement, and the possibility of a First Amendment safe harbor for truthful off-label speech. Finally, the Article will provide concluding remarks.

I. Off-Label Promotion Enforcement – The Regulatory Framework

As noted above, the phrase "off-label promotion" is not found anywhere in the Food, Drug, and Cosmetic Act of 1938 ("FDCA"), the statutory framework under which

---

8 The authors' law firm, King & Spalding LLP has had significant involvement in arguing for Constitutional protection of truthful off-label promotional speech. *See, e.g.*, *infra* note 60.

9 *See* Osborn, *supra* note 6, at 314, n.45 (noting that "[k]ey government prosecutors have confirmed that it does not matter whether or not the questionable speech is truthful or misleading, so long as it is 'off-label.'") (citing statements made by Assistant United States Attorney Michael Loucks at an industry-sponsored panel).

10 *Id.* at 327-29.

11 __ F.3d __, 2012 WL 5992141, *15 (2d Cir. Dec. 3, 2012).

12 The FDA has indicated that it will not appeal the *Caronia* decision. *See* Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J., Jan. 23, 2009. In fact, in a panel presentation at the 2013 ABA White Collar Conference, the head of the FDA's Office of Criminal Investigation stated that in the wake of the Caronia decision, his office had reviewed its investigations from previous years and concluded that all of them involved conduct that would still be actionable after Caronia. *See* Nate Raymond, *Lawyers Debate Impact of 2nd Circuit Off-Label Ruling*, Legal Monitor Worldwide (March 12, 2013), 2013 WLNR 6142345.

the FDA draws its authority to regulate the sale and marketing of pharmaceutical drugs. Instead, the FDA's authority to regulate off-label promotion is drawn from the FDCA's prohibitions against introducing an "unapproved new drug" or a "misbranded" drug into interstate commerce.[13] In this regard, the FDCA grants the FDA wide latitude in regulating a drug's "labeling" to ensure that it is not false or misleading.[14] The term "labeling" is defined broadly to include "all labels and other written, printed, or graphic matter . . . accompanying such article."[15] If a manufacturer promotes a drug for a use not contained in the FDA-approved labeling, the FDA considers the drug a "new drug" insofar as it has not been deemed safe and effective "for use under the conditions prescribed, recommended, or suggested in the labeling."[16] In this regard, even though the FDCA's definition of "labeling" is broad, the FDCA's implementing regulations define "labeling" even further to include virtually any tangible material created or disseminated by a manufacturer discussing a particular drug.[17] As one commentator has noted, therefore, "the Act's prohibition of false or misleading labeling is transformed by the agency into an effective prohibition on any advertisement, promotional message, or discussion that is not consistent with the approved product labeling, or otherwise concerns any use that has not been approved expressly by the FDA, regardless of whether it is truthful or accurately reflects good medical practice."[18]

In addition to proscribing the introduction of an unapproved new drug into interstate commerce, the FDCA also makes it a crime to introduce a "misbranded" drug. A drug is misbranded if, *inter alia*, its labeling fails to bear "adequate directions for use."[19] FDA regulations define "adequate directions for use" as "directions under which the layman can use a drug safely and for the *purpose for which it is intended*."[20] Accordingly, the FDA regulations transform the statutory term "use" into "intended use" which is determined by reference to "the objective intent of the persons legally responsible for the labeling of drugs."[21] Intended use may be demonstrated by "oral or written statements by such persons or their representatives" and "the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised."[22] The FDA requires, therefore, that each intended use be approved by the agency, and if the intended use has not been approved, then it takes the position that the manufacturer has introduced a misbranded drug into interstate commerce.

The FDCA contains no private right of action, and as a result, only the federal government can bring actions for violations of the Act. Off-label promotion investigations often go hand-in-hand, however, with actions under the federal False Claims Act (FCA), which contains a *qui tam* provision allowing private individuals to file actions on behalf of the United States. Enacted during the Civil War, the FCA subjects to civil liability "[a]ny person who knowingly presents or causes to be presented, to . . . the United States Government . . . a false or fraudulent claim for payment or approval," as well as "[a]ny person who knowingly makes, uses, or causes to be made or used a false record or statement to get a false or fraudulent claim paid or approved by the Government."[23] As one court has noted, the *qui tam* provision of the Act served to "unleash[ ] a posse of *ad hoc* deputies to uncover and prosecute frauds against the government."[24]

13 *See* 21 U.S.C. §§ 331(a), (d).
14 *See id.* § 352(a).
15 *Id.* § 321(m).
16 *Id.* § 321(p).
17 *See* 21 C.F.R. § 202.1.
18 Osborn, *supra* note 6, at 308-09 (internal quotations and citations omitted).
19 21 U.S.C. § 352(f).
20 21 C.F.R. § 201.5 (emphasis added).
21 *Id.* § 201.128.
22 *Id.*
23 31 U.S.C. §§ 3729(a)(1)-(2).
24 United States ex rel. Wilson v. Graham County Soil & Water Conservation Dist., 528 F.3d 292, 298 (4th Cir. 2008).

In the context of off-label promotion, many (if not most) investigations have been fueled by whistleblowers who file suit under the *qui tam* provisions of the FCA and who hope to receive a substantial share of any subsequent government recovery.[25] These suits rely on an underlying violation of the FDCA, and typically allege that: (1) the manufacturer engaged in an illegal scheme to market off-label uses of a drug or device in violation of the FDCA; and (2) as a result of the off-label promotional campaign, false claims for payment were submitted to federal healthcare programs such as Medicare and Medicaid, which did not provide coverage for the off-label use in question.[26] As noted, 2012 was a record year for recoveries under the FCA, and health care fraud recoveries accounted for over $3 billion.[27] Use of the FCA in prosecuting off-label promotion in particular has been a cornerstone of the government's health care fraud initiative, and the number of off-label enforcement actions have increased concomitantly with the expansion of the FCA generally.[28]

Given the government's expansive formulation of its prohibition against off-label promotion, and the various tools at its disposal to combat it, manufacturers are very aware of the risks of promoting drugs off-label and have implemented comprehensive compliance programs, yet nonetheless continue to find themselves in the government's cross-hairs. This begs the question of why? Briefly, beyond a few narrow exceptions allowing for the exchange of certain off-label scientific information,[29] there are no clear rules governing what information a manufacturer may legally disseminate.[30] Not only are there many uncertainties under the regulatory scheme, there is a general dearth of case law interpreting, and providing a check to, the government's position. This is partly the result of the fact that because most manufacturers are publicly-traded companies, they cannot afford, because of risk of the business loss and reputational damage, to litigate a criminal case to disposition. Moreover, manufacturers criminally convicted of off-label promotion face exclusion from federally-funded health care programs. For these reasons, therefore, nearly all enforcement actions levied against manufacturers end in settlement without a check on the enforcement agencies' interpretations of the rules through adversarial process and without a court decision regarding the agencies' views. This lack of open process also has meant that manufacturers seeking to learn from recent enforcement actions have not been privy to the underlying settlement negotiations, and only have been able to glean relevant information regarding the rules from the few available public materials. As one commentator recently noted, the lack of judicial review in these cases has caused "a cyclical loosening of the kinds of facts that get introduced during these cases as evidence of promotion," as a result of the fact that "prosecutors have grown accustomed to the fact that they are unlikely to face court challenges in these cases."[31]

Because of aggressive enforcement and the tremendous costs and risks stemming from even facing a government investigation, manufacturers have instituted rigorous compliance programs designed to prevent and deter illegal off-label promotional activities. This has necessarily reduced the number of glaring infractions available to the government

---

25 *See, e.g.*, David J. Ryan, *False Claims Act: An Old Weapon with New Firepower is Aimed at Health Care Fraud*, Annals of Healthcare Law 4 (1995).
26 *See* Edward P. Lansdale, *Used As Directed? How Prosecutors Are Expanding the False Claims Act to Police Pharmaceutical Off-Label Marketing*, 41 New Eng. L. Rev. 159, 187-89 (2006).
27 *See supra* note 3.
28 *See* Osborn, *supra* note 6, at 312.
29 *See* discussion *infra* at Section III.
30 *See* Osborn, *supra* note 6, at 317.
31 Scott Gottlieb, M.D., *The U.S. Department of Justice's Targeting of Medical Speech and its Public Health Impacts*, AMERICAN ENTERPRISE INSTITUTE FOR PUBLIC POLICY RESEARCH, HEALTH POLICY OUTLOOK 4-5 (Dec. 2012), *available at* http://www.aei.org/files/2012/12/06/-the-us-department-of-justices-targeting-of-medical-speech-and-its-public-health-impacts_084900709055.pdf.

to investigate. In response, the government has expanded further their areas of scrutiny and taken more aggressive positions regarding the scope of the FCA and the FDCA's prohibition against off-label marketing. In particular, as the next Section details, prosecutors are increasingly branching out from the traditional sales and marketing aspects of off-label promotion and are now peeking under the hood of clinical research and other aspects of the scientific exchange process.

II. The Trend Towards Scrutiny of Clinical Data and the Scientific Exchange Process

In announcing the $3 billion settlement reached between DOJ and GlaxoSmithKline resolving allegations of off-label promotion of the drugs Paxil and Welbutrin, Deputy Attorney General James Cole announced that in the three years prior, DOJ had "recovered a total of more than $10.2 billion in settlements, judgments, fines, restitution and forfeiture in health care fraud matters."[32] Earlier in 2012, Attorney General Eric Holder testified that for every dollar spent combating health care fraud, the government recoups an average of seven dollars.[33] This return on investment is a key driver of the government's focus on health care fraud, and the government understandably enjoys touting its recoveries. As much of the low-hanging fruit has already been picked, however, and in order to maintain its high return on investment, DOJ has been forced to adopt more aggressive enforcement efforts and theories. In particular, recent settlement agreements and corporate integrity agreements show that prosecutors have begun to focus beyond the actions of sales representatives to manufacturers' medical affairs and clinical research activities.

Several manufacturers are now under investigation for allegedly misrepresenting or failing to disclose clinical trial data. In this regard, prosecutors and plaintiffs' attorneys allege that the sale of an FDA-approved drug based on a misrepresented clinical study, is, by definition, a false claim. For example, in May 2012, DOJ announced a $1.5 billion settlement with Abbott Laboratories over the illegal off-label promotion of the drug Depakote.[34] Abbott pleaded guilty to misbranding Depakote to treat schizophrenia, an indication that was not approved by the FDA. Summarizing one section of the agreed statement of facts contained in the guilty plea, the DOJ press release noted the following:

> Abbott funded two studies of the use of Depakote to treat schizophrenia, and both failed to meet the main goals established for the study. When the second study failed to show a statistically significant treatment difference between antipsychotic drugs used in combination with Depakote and antipsychotic drugs alone, Abbott waited nearly two years to notify its own sales force about the study results and another two years to publish those results.[35]

The delay in the disclosure of clinical study data served as one basis on which DOJ based its off-label promotion claims. Moreover, even after Abbott revised presentation materials to include slides containing information on the disappointing study, the agreed statement of facts from the company's guilty plea states that Abbott also "included approximately a dozen slides about other [positive] studies . . . and slides about when healthcare providers

32 DOJ Press Release, Deputy Attorney General James M. Cole Speaks at the GSK Press Conference (July 2, 2012), *available at* http://www.justice.gov/iso/opa/dag/speeches/2012/dag-speech-1207021.html.
33 DOJ Press Release, Attorney General Eric Holder Testifies Before the U.S. House of Representatives Committee on Appropriations Subcommittee on Commerce, Justice, Science, and Related Agencies (Feb. 28, 2012), *available at* http://www.justice.gov/iso/opa/ag/speeches/2012/ag-speech-1202281.html.
34 DOJ Press Release, Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-Label Promotion of Depakote (May 7, 2012), *available at* http://www.justice.gov/opa/pr/2012/May/12-civ-585.html.
35 *Id.*

should use Depakote to treat agitation and aggression in elderly dementia patients and how to dose Depakote for this off-label use."[36] Accordingly, the Abbott settlement indicates that, aside from the more overt off-label promotional tactics that have been the cornerstone of DOJ's enforcement efforts, DOJ will now consider the presentation of positive, without available negative, clinical data evidence of off-label marketing – more to the point, and as will be discussed *infra*, at least in the Abbott case, the dissemination of positive without negative data was considered "misleading" by DOJ.

Similarly, the criminal information filed against GlaxoSmithKline (GSK) relating to the off-label investigation of Paxil further illustrates DOJ's new scrutiny of manufacturers' failures to disclose clinical study design and data.[37] In this case, DOJ alleged that GSK hired a contractor to write an article analyzing the results of a clinical study. According to DOJ, the article, which was published in a peer reviewed publication, was false and misleading because "the article's text identified the two primary endpoints . . . [but] the article never explicitly stated that [the clinical study] failed to demonstrate efficacy on either of its primary endpoints."[38] Furthermore, GSK sent the offending article to its sales representatives with an attached cover memorandum. According to DOJ, the cover memorandum misrepresented that the clinical trial of Paxil demonstrated efficacy insofar as it did not explicitly state that the study failed to meet its protocol-defined primary and secondary endpoints, and in addition, failed to notify the sales team that GSK had conducted to other studies that also failed to demonstrate Paxil's efficacy.[39]

As evidenced by DOJ's allegations against Abbott and GSK, it is clear that off-label investigations have delved far beyond more traditional off-label promotional activities, and that the government is now analyzing the actual clinical study protocols and intended primary endpoints of post-market clinical studies. Moreover, law enforcement's clinical focus can now be routinely found in corporate integrity agreements ("CIAs") entered into between settling companies and the Office of the Inspector General ("OIG") of the Department of Health and Human Services. Like DOJ's increased focus on clinical and research activities, OIG has expanded related obligations in recent CIAs, including clinical research-related provisions even in cases in which allegations relating to clinical research are not included in the underlying settlement documents.

More specifically, recent CIAs contain provisions imposing obligations related to clinical studies and research including *inter alia*: (1) designation of personnel involved in post-market clinical studies as "Relevant Covered Persons;" (2) management certifications by senior management responsible for clinical research; (3) adoption of clinical study policies and procedures; (4) the imposition of research and publication controls; (5) monitoring of researchers; and (6) various transparency requirements.[40] Recent CIAs also typically require

36 Agreed Statement of Facts at 17, United States v. Abbott Laboratories, No. 12-cr-00026-SGW (W.D. Va. May 7, 2012).
37 Criminal Information, United States v. GlaxoSmithKline, LLC, (D. Mass. June 2012) *available at* www.justice.gov/opa/documents/gsk/gsk-criminal-info.pdf (hereinafter, "GSK Criminal Information"); *see also* DOJ Press Release, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012), *available at* http://www.justice.gov/opa/pr/2012/July/12-civ-842.html.
38 GSK Criminal Information at ¶ 34, *surpa* note 37.
39 *Id.* at ¶¶ 38-40.
40 *See, e.g.*, Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Amgen, Inc., U.S. Dep't Health & Hum. Servs. Off. Inspector Gen. (Dec. 14, 2012), https://oig.hhs.gov/fraud/cia/agreements/Amgen_12142012.pdf; Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Boehringer Ingelheim Pharmaceuticals, Inc., U.S. Dep't Health & Hum. Servs. Off. Inspector Gen. (Oct. 22, 2012), https://oig.hhs.gov/fraud/cia/agreements/Boehringer_Ingelheim_Pharmaceuticals_10222012.pdf; Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and GlaxoSmithKline, LLC., U.S. Dep't Health & Hum. Servs. Off. Inspector Gen. (June 28, 2012), https://oig.hhs.gov/fraud/cia/agreements/GlaxoSmithKline_LLC_06282012.pdf; Corporate Integrity Agreement Between the Office of Inspector General of the Department of Health and Human Services and Abbott Laboratories, U.S. Dep't Health & Hum. Servs. Off. Inspector Gen. (May 7, 2012), https://oig.hhs.gov/fraud/cia/agreements/Abbott_Laboratories_05072012.pdf.

the engagement of a Independent Review Organization ("IRO") to perform various systems and transaction reviews, including reviews of clinical research and publication activities[41] – an onerous requirement that further indicates the trend towards extensive oversight and intervention in the medical affairs and clinical research functions of manufacturers.

By way of example, the recent Amgen, Inc. CIA contains all of the above-mentioned provisions – and further evidences DOJ's scrutiny of post-market clinical research.[42] Moreover, the Criminal Information filed against Amgen and the DOJ Press Release announcing the settlement introduce a new enforcement theory related to clinical research – "reactive marketing." According to the Amgen Criminal Information, Amgen sales representatives were provided with clinical research articles supporting the off-label use of the drug in question, Aranesp.[43] The sales representatives were trained to elicit questions from doctors relating to off-label use of Aranesp, which would provide the reps the "necessary cover" to then give the doctors the off-label studies.[44] According to DOJ, those off-label studies had been rejected by FDA as "insufficient to support the safety and efficacy of those off-label uses."[45]

Taken together, these trends show that DOJ and OIG are seeking ever more tools in CIAs in their quest to root out what they see as off-label promotion. These trends also evidence the growing distrust the government has of manufacturers' post-market clinical research and publication, particularly scrutiny of clinical study design, primary and secondary endpoint analysis, and disclosure (or lack of such) of clinical study results. As discussed in the next section, however, manufacturers now may have a First Amendment argument that can auger the rise of a safe harbor for truthful off-label promotion, or at the very least provide manufacturers with greater leverage in future settlement negotiations.

III. The Intersection of the First Amendment and Truthful Off-Label Promotion

A. The Legal Framework

It is well recognized that the FDCA's misbranding provisions, and the FDA's accompanying regulations impose substantial limitations on manufacturer's ability to speak about off-label uses of their products. What is less clear, however, is precisely the type of speech proscribed by the misbranding provisions, current FDA regulations and the agency's interpretation of those regulations. In this regard, there is no clear line between illegal off-label promotion and the legitimate exchange of scientific information – and manufacturers have been forced to grapple with regulators who have broad authority to condemn off-label promotion, but who have never clearly defined what constitutes "promotion."

While FDA has broad authority to regulate the dissemination of information about prescription drugs, it is not empowered to regulate the practice of medicine, and physicians are free to prescribe drugs for off-label uses.[46] Indeed, as the FDA itself has

41 *See, e.g.,* Amgen CIA, *supra* note 40, at pp. 12-13, 25-26; Abbott Laboratories CIA, *supra* note 40, at pp. 15-16. In most recent CIAs OIG had the authority to select up to three specified areas of review, but in the Amgen and Abbott CIAs, OIG included "Research and Publications Activities" as stand-alone areas for required transaction testing (in addition to the three additional areas of review).

42 *See* Amgen CIA, *supra* note 40; DOJ Press Release, Amgen, Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations (Dec. 19, 2012), *available at* http://www.justice.gov/opa/pr/2012/December/12-civ-1523.html; Criminal Information, United States v. Amgen, Inc., No. 12-cr-00760-SJ (E.D.N.Y. Dec. 18, 2012)

43 Amgen Criminal Information, *supra* note 42.

44 *Id.*

45 Amgen DOJ Press Release, *supra* note 42.

46 *See* 21 U.S.C. § 396 (providing that the FDCA does not "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").

acknowledged, in certain situations off-label use of drugs "may even constitute a medically recognized standard of care."[47] Moreover, in light of the fact that off-label use is a common and often necessary practice, Congress and the Centers for Medicare & Medicaid Services ("CMS") actually mandate federal reimbursement for off-label uses of drugs listed in medical compendia.[48]

Against this backdrop, and in apparent recognition of the legitimate off-label uses of drugs and devices, the FDA has recognized that because physicians require "objective, balanced, and accurate information of important unapproved uses of approved products," the public interest is best served with the "earlier dissemination" of truthful, accurate, and non-misleading off-label information.[49] In that regard, the FDA has promulgated a few limited exceptions to its general proscription against sharing off-label information with health care providers. The few "exceptions" allowing limited scientific exchange of off-label information, however, are often too vague, too narrow, and are promulgated in the form of "non-binding" guidance documents – leaving manufacturers either overly cautious and gun-shy of actually utilizing the available exceptions for fear that their actions could be used as evidence of off-label promotion or potentially raise the risk of enforcement action.[50]

By way of example, non-binding[51] FDA guidance allows manufacturers to disseminate copies of peer-reviewed journal articles discussing clinical trial results for off-label uses,[52] but the manufacturer could be subject to investigation or prosecution if the underlying research contained in the article is summarized – even truthfully – by the manufacturer. Moreover, although it has never clearly stated its position on the matter, FDA policy appears to allow manufacturers to discuss off-label information in response to unsolicited requests,[53] and would appear to allow manufacturers to disseminate "safety warnings" that do not promote, but rather discourage, off-label use of their products.[54] In other words, the FDA has never clearly articulated its position regarding what constitutes permissible "scientific exchange" and what constitutes impermissible "promotion," – and the only thing manufacturers can be certain of, is that statements concerning the efficacy of their products will only be deemed truthful and not misleading if the FDA has specifically included those claims in the approved labeling of the product at issue.

This regulatory uncertainty is complicated by the significant First Amendment free speech concerns attendant to any prohibition on the dissemination of truthful non-misleading scientific information. FDA's authority to regulate off-label promotional speech was constitutionally circumscribed to some degree by the Washington Legal Foundation (WLF) cases of the late 1990s.[55] In those cases, the WLF, a public interest group that

47 Good Reprint Practices, *supra* note 6.
48 *See* 42 U.S.C. § 1396r-8(k)(6) (Medicaid); Medicare Benefit Policy Manual, Ch. 15, § 50.1.2 (Medicare); *see also* Dep't of Health & Hum. Servs., Charter: Medicare Evidence Development & Coverage Advisory Committee (Nov. 12, 2008), *available at* http://www.cms.hhs.gov/FACA/Downloads/medcaccharter.pdf (discussing CMS authorization of federal reimbursement of products for off-label uses after manufacturer submission of medical information regarding such use).
49 *See* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics and Devices, 63 Fed. Reg. 64,556, at 64,579 (Nov. 20, 1998).
50 *See* Gottlieb, *supra* note 31.
51 *See* 21 C.F.R. § 10.115(d)(1) (2009) ("Guidance documents do not establish legally enforceable rights or responsibilities.").
52 *See* Good Reprint Practices, *supra* note 6.
53 *See* Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994); *United States v. Stevens*, No. 10-cr-0694 (D. Md. 2011), Tr. 90:10-22 (Apr. 27, 2011) (testimony of FDA official Sandeep Saini). The authors' law firm represented the defendant in the Stevens case.
54 *See Allergan v. United States*, No. 09-cv-1879-JDB (D.D.C.), United States' Reply in Support of Motion to Dismiss, Dkt. No. 37, at 7 (Mar. 29, 2010).
55 *See Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), amended by 36 F. Supp. 2d 16 (D.D.C. 1999), dismissed and vacated in part sub. nom. *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *see also* Erin E. Bennett, Comment, Central Hudson-Plus: Why Off-Label Pharmaceutical Speech Will Find Its Voice, 49 Hous. L. Rev. 459, 470-72 (2012) (discussing the history of the WLF litigation); John Kamp, *FDA Marketing v. First Amendment*: Washington Legal Foundation Legal Challenges to Off-Label Policies May Force Unprecedented Changes at FDA, 54 Food & Drug L. J. 555 (1999).

advocates for, among other things, limited government and free enterprise, challenged the FDA's restrictions on the distribution of certain truthful and non-misleading scientific and medical information. In these cases, FDA guidance curtailing the distribution of scientific publications distributed to medical professionals was deemed an unconstitutional infringement of commercial speech under the rubric of the Supreme Court's Central Hudson four-part commercial speech test.[56] While it is beyond the scope of this Article to discuss the WLF litigation in any great detail, it is sufficient to note that the FDA avoided a permanent injunction curtailing enforcement of its guidance by stipulating to certain "safe harbors" established by the WLF ruling.[57]

Notwithstanding the fact that the First Amendment concerns surrounding the FDA's policies have received extensive critique and commentary by academics and other interested parties,[58] many manufacturers have been unwilling to advance First Amendment arguments regarding truthful off-label commercial speech for fear of prejudicing their position in their negotiations with DOJ and FDA. Manufacturers' unwillingness, however, has receded a bit. In recent years, at least two manufacturers have taken the "extraordinary"[59] step of filing declaratory judgment actions against FDA seeking a determination that the First Amendment protects truthful off-label speech.[60] Neither of those actions, however, have been litigated by the manufacturers to a point that yielded a judicial decision.

---

56 *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York*, 447 U.S. 557 (1980). Under the test articulated in Central Hudson, first, the speech in question must concern lawful activity and must not be misleading in order to garner First Amendment protection. Second, the governmental interest asserted to justify the restriction on speech must be substantial. Third, the restriction must directly advance the governmental interest "to a material degree," and fourth, the restriction must be "narrowly drawn" and not more extensive than necessary to serve the government interest. *United States v. Caronia*, __ F.3d __, 2012 WL 5992141, at *11 (2d Cir. Dec. 3, 2012) (describing the Central Hudson test in the context of off-label promotion and scientific exchange).

57 *See* Osborn, *supra* note 6, at 312; Bennett, *supra* note 55, at 471-72.

58 *See, e.g.*, *id.*; Briana R. Barron, Comment, Silent Warning: the FDA's Ban on Off-Label Speech; Is It Protecting Our Safety?, 94 Marq. L. Rev. 983 (2011); Aaron S. Kesselheim, Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech, 37 Am. J. L. & Med. 225 (2011); Jacob Rogers, Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses, 76 Geo. Wash. L. Rev. 1429 (2008); Ralph F. Hall, Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans, 62 Food & Drug. L. J. 1 (2007); David M. Fritch, Speak No Evil, Hear No Evil, Harm the Patient? Why the FDA Needs to Seek More, Rather Than Less, Speech From Drug Manufacturers on Off-Label Drug Treatments, 9 Mich. St. U. J. Med. & L. 315 (2005); A. Elizabeth Blackwell, Drug Manufacturers First Amendment Right to Advertise and Promote Products for Off-Label Use; Avoiding a Pyrrhic Victory, 58 Food & Drug L. J. 439 (2003).

59 *See* Osborn, *supra* note 6, at 329.

60 *See* Allergan v. United States, No. 09-cv-1879-JDB (D.D.C.); Johnathan D. Rockoff, *Allergan Suit Seeks to Lift Botox Curbs*, WALL ST. J., Oct. 2, 2009, at B4; Natasha Singer, *Botox Maker's Suit Cites Free Speech*, N.Y. TIMES, Oct. 2, 2009, at B3. In September, 2010, as part of a criminal and civil investigation, Allergan dismissed its lawsuit and stated:

> To resolve [a] criminal and civil investigation, Allergan was required by the Government to dismiss Allergan's First Amendment lawsuit pending in Washington, D.C., in which Allergan sought a ruling that it could proactively share truthful scientific and medical information with the medical community to assist physicians in evaluating the risks and benefits if they choose to use [Allergan's drug] off-label. . . . Allergan is disappointed that the court was not afforded an opportunity to hear and rule on these important First Amendment issues, as Allergan believes that physicians, patients, manufacturers, payers, and ultimately the quality of evidence-based medicine itself would have benefited from a ruling clarifying the law.

Allergan, News Release: Allergan Resolves United States Government Investigation of Past Sales and Marketing Practices Relating to Certain Therapeutic Uses of Botox (Sept. 1, 2010). The authors' law firm represented Allergan in its declaratory judgment action.

See also Par Pharmaceutical, Inc. v. United States, No. 11-cv-1820-RWR (D.D.C.). Echoing the First Amendment suit filed by Allergan, Par Pharmaceutical, Inc. sued FDA seeking declaratory judgment and injunctive relief against FDA's criminalization of truthful and non-misleading off-label speech as a violation of the First Amendment. The company argued that the "threat of prosecution for alleged off-label promotion based on Par's truthful and non-misleading speech to healthcare professionals concerning the FDA-approved use of Par's FDA-approved prescription drug currently chills Par's speech." Par asserted that the government is maintaining an inconsistent approach to off-label uses: criminalizing the manufacturers' discussion of off-label uses while often acknowledging the uses' clinical importance and reimbursing for them under Medicare and Medicaid. Recently, on March 5, 2013, Par pleaded guilty to a single criminal misdemeanor for misbranding Megace ES in violation of the FDCA and agreed to pay $45 million to resolve its criminal and civil liability. Importantly, Par's plea agreement required it to dismiss with prejudice its declaratory judgment action – thereby eliminating the prospect of a judicial ruling on the merits of the First Amendment question. *See* DOJ Press Release, Par Pharmaceuticals Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (Mar. 5, 2013), *available at* http://www.justice.gov/opa/pr/2013/March/13-civ-270.html; *see also* King & Spalding Client Alert, *Two New Developments in First Amendment Challenges to Off-Label Promotion: What's Next* (March 13, 2013), *available at* http://www.kslaw.com/imageserver/KSPublic/library/publication/ca031313.pdf.

Instead, it has taken the litigating of the issue in a criminal case against a manufacturer's employee to gain a written decision regarding the First Amendment. On December 3, 2012, the United States Court of Appeals for the Second Circuit issued a decision in the case of *United States v. Caronia* finally addressing First Amendment arguments on the merits. The court concluded that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[61] Hailed by some as a landmark decision, the *Caronia* decision potentially ushers in a new era of FDA off-label enforcement. Before discussing the implications of the opinion, however, a brief background on the case is in order.

B. United States v. Caronia

On December 3, 2012, a majority panel of the Second Circuit overturned the November 2009 misdemeanor conviction of Alfred Caronia for conspiracy to introduce misbranded drugs into interstate commerce by promoting the drug Xyrem for off-label use in violation of the FDCA. Xyrem, a central nervous system depressant, was approved in 2002 for the treatment of a subset of narcolepsy patients. The drug's label contained a boxed warning stating that safety and efficacy had not been established in patients under sixteen years of age.

Caronia's conviction was premised on verbal off-label promotional statements he made while working as a Specialty Sales Consultant for Orphan Medical, Inc. ("Orphan").[62] More specifically, Caronia promoted Xyrem for a variety of unapproved indications and subpopulations, including insomnia, muscle disorders, chronic pain, fibromyalgia, Parkinson's, and in patients under sixteen years of age. The government initiated the investigation in 2005 after a former salesperson filed a *qui tam* suit against the company. During the course of the investigation, Caronia was tape-recorded on two occasions discussing off-label uses of Xyrem with Dr. Peter Gleason, a paid physician speaker. Dr. Gleason and Caronia were recorded discussing off-label uses of the drug with Dr. Jeffrey Charo, an undercover government informant, and in 2006, the government filed charges against Caronia, Dr. Gleason, Orphan, and David Tucker, a former Orphan sales manager. In March 2007, Tucker pleaded guilty to a single felony misbranding charge. In July 2007, Orphan pleaded guilty to felony charges, and its parent company, Jazz Pharmaceuticals, Inc. agreed to pay $20 million and enter into a Corporate Integrity Agreement to resolve both criminal and civil charges.[63] Dr. Gleason pleaded guilty to criminal misbranding charges in August 2008.

Caronia did not plead guilty, and prior to trial moved to dismiss the charges against him on First Amendment grounds. The trial court denied Caronia's motion. While recognizing that Caronia raised issues "very much unsettled, not only in this circuit but nationwide," the court ultimately concluded that the FDCA's criminalization of off-label promotional speech was constitutional insofar as it was not more extensive than necessary to achieve FDA's objective.[64]

---

61 *United States v. Caronia*, __ F.3d __, 2012 WL 5992141, at *15 (2d Cir. Dec. 3, 2012).

62 Orphan Medical, Inc. was purchased by Jazz Pharmaceuticals, Inc. in 2005. The authors' law firm represented Jazz Pharmaceuticals/Orphan Medical throughout the course of the government's investigation, as well as during the prosecution of Alfred Caronia. King & Spalding continues to represent the Company.

63 *See* DOJ Press Release, Jazz Pharmaceuticals, Inc. Agrees to Pay $20 Million to Resolve Criminal and Civil Allegations in "Off-Label" Marketing Investigation (July 13, 2007), *available at* http://www.justice.gov/usao/nye/pr/2007/2007jul13a.html.

64 *See United States v. Caronia*, 576 F. Supp. 2d 385 (E.D.N.Y. 2008).

Caronia was tried to a jury in October 2008, and was subsequently found guilty of one count of conspiracy to introduce a misbranded drug into interstate commerce. Caronia appealed his conviction to the Second Circuit, arguing that the First Amendment protects truthful and non-misleading promotional speech of an FDA-approved drug for off-label indications. The Second Circuit agreed.

The majority opinion, authored by Judge Denny Chin, first questioned whether Caronia's off-label promotional statements were used as evidence of Xyrem's intended use, as argued by the government, or whether Caronia was prosecuted "only for promoting an FDA-approved drug for off-label use."[65] Citing the Supreme Court's Wisconsin v. Mitchell decision,[66] the court assumed without deciding that off-label promotion could evidence a drug's intended use. After thoroughly examining the prosecutors' trial statements as well as the jury instructions, however, the court concluded that the trial record "confirms overwhelmingly that Caronia was, in fact, prosecuted and convicted for promoting Xyrem off-label."[67] The court noted that "[t]he government never argued in summation or rebuttal that the promotion was evidence of intent," and "never suggested that Caronia engaged in any form of misbranding other than [off-label] promotion."[68] In that regard, the court concluded that the government "clearly prosecuted Caronia for his words – for his speech" and that the trial court's jury instructions "led the jury to believe that Caronia's promotional speech was, by itself, determinative of his guilt."[69] Citing the Supreme Court's 2011 Sorrell v. IMS Health, Inc. decision for the proposition that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment,"[70] the Second Circuit concluded that heightened scrutiny should apply to the government's interpretation of the FDCA's criminalization of off-label promotional speech.

The court then determined that the government's position was both content and speaker based: content based because the government's interpretation of the misbranding provisions permits "speech about the government-approved use of drugs" while prohibiting "certain speech about the off-label use of drugs," and speaker based because the provisions "target[ ] one kind of speaker – pharmaceutical manufacturers – while allowing others to speak without restriction."[71] Accordingly, the government's interpretation of the FDCA's misbranding provisions could not pass constitutional muster, and Caronia's prosecution failed the strict scrutiny test.

Next, the court concluded that even if off-label promotional speech triggered only intermediate scrutiny, Caronia's prosecution nevertheless failed this lower threshold. Under the four-part Central Hudson test for commercial speech,[72] the court found the first two prongs to be "easily satisfied" insofar as the off-label speech in question concerned lawful activity and off-label speech is "not in and of itself false or misleading."[73] Moreover, the court determined that the government's interest in "preserving the effectiveness and integrity of the FDCA's drug approval process, and [its] interest in reducing patient exposure to unsafe and ineffective drugs" was substantial.[74]

---

65 Caronia, 2012 WL 5992141, at *8.
66 508 U.S. 476, 489 (1993) (holding that the First Amendment does not prohibit the use of speech to establish intent).
67 Caronia, 2012 WL 5992141, at *9.
68 *Id.*
69 *Id.*
70 131 S. Ct. 2653, 2659 (2011).
71 Caronia, 2012 WL 5992141, at *12.
72 *See supra* note 56.
73 Caronia, 2012 WL 5992141, at *13.
74 *Id.*

Turning to the third and fourth prongs of the Central Hudson test, the court determined that because physicians can legally prescribe, and patients can legally receive, drugs off-label, "it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals."[75] Describing the government's position as "paternalistic," the court held that "the government's prohibition of off-label promotion by pharmaceutical manufacturers 'provides only ineffective or remote support for the government's purpose'" and, therefore, failed the third prong of the Central Hudson analysis.[76] Finally, with respect to the last prong of the test, the court held that the government's imposition of a "complete and criminal ban on off-label promotion by pharmaceutical manufacturers" was not narrowly tailored to protect the government's interests. Citing several less-restrictive methods of restricting off-label promotional speech, the court concluded "that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[77]

In a vigorous dissenting opinion, Judge Debra Ann Livingston argued that the majority's decision "calls into question the very foundations of our century-old system of drug regulation."[78] Judge Livingston would have upheld Caronia's conviction on the ground that his off-label promotional speech served only as evidence of the drug's intended use – which the First Amendment does not prohibit – thereby avoiding the constitutional conundrum. In making this determination, however, the dissent never addressed the central point of the majority's opinion – that in this case, Caronia was prosecuted and convicted for "mere off-label promotion."[79] Next, even assuming Caronia was entitled to some level of First Amendment protection, Judge Livingston would have upheld his conviction under the Central Hudson test for commercial speech.[80] Aligning with the majority, the dissent concluded that, the prohibition of off-label speech directly advanced a substantial government interest – ensuring that drugs regulated by the FDA are safe and effective.[81] Then, with little analysis, the dissent summarily concluded that the ban on truthful off-label promotion – only applicable to drug manufacturers – "directly advances" this interest because only drug manufacturers could "undermine the [FDA] approval process by not participating in it."[82] Finally, the dissent would have concluded that the prohibition on off-label promotion was narrowly tailored because drug manufacturers "are the precise group that the government must encourage to participate in the [FDA] approval process."[83] In that regard, Judge Livingston concluded that "[t]he prohibition of off-label promotion is thus not simply a 'paternalistic' attempt to shield physicians and patients from truthful information," and would have found it constitutional because, even if the regulation directly regulates speech, it is narrowly tailored to advance a substantial government interest.[84]

---

75 *Id.*
76 *Id.* at *13, 14.
77 *Id.* at *15. The less restrictive alternatives of restricting off-label speech cited by the court include, *inter alia*, developing warning or disclaimer systems or safety tiers for the off-label market, capping off-label prescriptions, imposing non-criminal penalties, or banning off-label use of drugs in certain circumstances. *See id.*
78 *Id.* at *15 (Livingston, J., dissenting).
79 *Id.* at *8.
80 Importantly, Judge Livingston's dissent failed to address "heightened scrutiny" under *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011), which was a separate and independent basis for the majority's decision. *See* Caronia, 2012 WL 5992141, at *12-13.
81 *Id.* at *23 (Livingston, J., dissenting); *id.* at *13 (Chin, J.) (noting that "preserving the effectiveness and integrity of the FDCA's drug approval process" satisfied the fist prong of the Central Hudson analysis).
82 *Id.* at *24 (Livingston, J., dissenting).
83 *Id.*
84 *Id.* at *25.

C. Caronia – Potential Next Steps

Before addressing the potential implications of the *Caronia* decision, it is important to note that the decision does not all of a sudden permit manufacturers to engage in truthful off-label promotion. First, the opinion is only binding law in the Second Circuit, encompassing New York, Connecticut, and Vermont. In that vein, the *Caronia* case was not a declaratory judgment action, and neither the FDA nor DOJ is enjoined from pursuing similar prosecutorial theories in other circuits – or even in the Second Circuit for that matter. Importantly, however, the government has decided not to appeal *Caronia*,[85] which was likely a calculated decision by the government to avoid a Supreme Court ruling embracing the *Caronia* First Amendment reasoning.[86] In that regard, even if the government does not fully embrace the opinion, it is likely to shift its focus to enforcement of only false or misleading promotional statements – or to situations where the off-label promotion at issue demonstrably caused patient harm.[87]

IV. *Caronia's* Implications – First Amendment Safe Harbor or Mere Leverage in Settlement Negotiations

In the wake of *Caronia*, can manufacturers expect a sea change in FDA enforcement activity surrounding off-label promotion? Reading the tea leaves in the immediate aftermath of *Caronia*, the tide does appear to be turning, but perhaps not to the extent manufacturers would like. First, given the high return on investment and the large settlements routinely announced by DOJ, it would be naïve to presume the government would simply abandon these high-profile and profitable cases. Similarly, manufacturers should not expect the *Caronia* decision to stem the tide of whistleblowers bringing off-label allegations to the attention of the government. Nevertheless, while the full impact of the Second Circuit's decision remains to be seen, it clearly represents a check to the government's current off-label enforcement theory. In addition, two recent events shed light on the ways government may approach enforcement in the wake of *Caronia*.

First, only two weeks after the *Caronia* decision was handed down, DOJ announced a $762 million settlement with Amgen, Inc. involving off-label promotion of

85 *See supra* note 12.

86 Had the government appealed, and the Caronia decision reached the Supreme Court, the authors believe the Court would affirm the decision for a variety of reasons. First, the six Justice Sorrell v. IMS majority spoke clearly on this issue in 2011 when the Court held that restrictions on commercial speech that are both content and speaker-based are subject to "heightened judicial scrutiny." *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2664 (2011). The Court's opinion, which dealt with a Vermont statute regulating a pharmaceutical marketing practice known as "detailing," attributed special value to commercial speech relating to public health issues, "where information can save lives." *Id.* Moreover, in Sorrell, the State of Vermont did not argue that detailing was false or misleading or would "prevent false or misleading speech . . . within the meaning of this Court's First Amendment precedents." *Id.* at 2672. While the FDA has, at times, defended its restrictions on off-label promotion on the ground that such promotion is often biased or misleading, given manufacturers' financial interests in making a sale, the cases are legion holding that off-label promotion is not inherently false or misleading. Second, regarding the truthfulness of the speech at issue in Caronia, the trial record establishes that Alfred Caronia was prosecuted for off-label promotion – not false or misleading off-label promotion – and the government never even attempted to establish falsity. *See* Caronia, 2012 WL 5992141, at *6-7. Third, in the Caronia prosecution, it does not appear as though the government took the First Amendment challenge seriously either before or during trial. In this regard, neither the majority opinion nor the dissent discuss any evidence in the record that could be used to support the proposition that banning truthful speech is essential to achieving the government's objectives. Finally, as far as criminal defendants go, Alfred Caronia is fairly sympathetic – essentially the victim of a sting operation, his off-label promotional statements caught on tape by the government never led to actual prescriptions being written, and nobody was injured as a result. After the seemingly more culpable defendants pleaded guilty, Mr. Caronia was sentenced to probation, fined a grand total of $25, and ordered to do community service. All in all, and in light of the Supreme Court's 2011 Sorrell decision, the Caronia case would appear to be strong vehicle in which to have the Court rule on the constitutionality of the government's prohibition on truthful off-label promotion.

87 *See* Brenda Sandburg, Off-Label Prosecutions Hinge On Patient Benefit, Government Attorneys Say, THE PINK SHEET (Mar. 11, 2013) (quoting two Assistant United States Attorneys for the proposition that federal prosecutors will not pursue off-label enforcement actions where the off-label use is the standard of care and where patient harm is not present) (available by subscription; copy on file with the authors).

the drug Aranesp.[88] Not only did the government secure the largest False Claims Act settlement by any biotechnology company to date, it also obtained from Amgen a guilty plea to a criminal charge of illegally introducing a misbranded drug into interstate commerce. Given the temporal proximity to the *Caronia* decision, the press release announcing the Amgen settlement is notable for how forcefully government regulators condemned the practice of off-label promotion, and for how forcefully the government indicated it would continue to police such activity. For example, DOJ Civil Division's Principal Deputy Assistant Attorney General stated that the Amgen settlement "reinforces the Department of Justice's commitment to cracking down on unlawful conduct by pharmaceutical companies."[89] The Acting U.S. Attorney in Brooklyn commented: "Today's settlement demonstrates our vigilance in protecting America's healthcare consumers and pursuing any corporation that seeks to profit by violating U.S. law. ... To all who might consider introducing misbranded drugs into the marketplace, you are on notice: we remain steadfastly committed to prosecuting such violations of law."[90] A representative from the FBI added that "[p]romoting drugs for unapproved purposes is beyond wrong; it jeopardizes the health and safety of the public." Finally, New York's Attorney General continued with the "clear" message that "[t]here are no excuses for illegally marketing off-label drugs ... biotechnology giants are not above the law, and [his] office will continue to ensure that prescriptions be written based on medical judgment – not profit motive."[91] Moreover, and apparently taking cues from the *Caronia* dissent, several regulators echoed statements made in Judge Livingston's dissent when they commented that "[w]hen drug companies improperly misbrand their products, they . . . undermine the federal health care system that protects all of us," and "[p]reserving the integrity of the pharmaceutical industry is important work."[92] Accordingly, with the record Amgen settlement coming close on the heels of the *Caronia* decision, regulators seem to be signaling that the decision will not put a brake on their efforts to police off-label promotion by manufacturers. Indeed, the day before DOJ announced the Amgen settlement, the Acting U.S. Attorney for the Eastern District of New York essentially dismissed the *Caronia* decision out of hand. Noting that the Amgen settlement involved a concerted plan by the company to promote its drug off-label, and that *Caronia* involved mere speech by a sales representative, the prosecutor concluded that "[i]t's a very different type of prosecution."[93]

Second, and on the opposite end of the spectrum, the recent Par Pharmaceutical settlement may presage the shifting balance of power between the government and drug manufacturers. As previously noted, Par sued the FDA seeking declaratory judgment and injunctive relief against FDA's criminalization of truthful and non-misleading off-label speech as a violation of the First Amendment.[94] In its complaint, Par disclosed that it has been under investigation for its promotion of the drug Megace ES since 2009, and on March 5, 2013 Par pleaded guilty to a criminal misdemeanor for misbranding the drug and agreed to pay $45 million to resolve its civil and criminal liability. The global resolution settled three whistleblower suits brought under the False Claims Act.[95] Par's plea agreement, however, required it to dismiss with prejudice its declaratory judgment action – thereby eliminating the prospect of a judicial ruling on the merits of the First Amendment

88 *See* Amgen Press Release, *supra* note 42.
89 *Id.*
90 *Id.*
91 *Id.*
92 *Id.*
93 Andrew Pollack and Mosi Secret, *Amgen Agrees to Pay $762 Million for Marketing Anemia Drug for Off-Label Use*, N.Y. TIMES, Dec. 18, 2012.
94 *See supra* note 60.
95 *See* DOJ Press Release, Par Pharmaceuticals Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (Mar. 5, 2013), *available at* http://www.justice.gov/opa/pr/2013/March/13-civ-270.html.

question. Much like the Allergan settlement, it would appear as though Par's First Amendment arguments – especially in light of the *Caronia* decision – may have provided additional leverage in the company's settlement discussions with the government.

Of course, too much can be read into the Amgen and Par settlements, but at a minimum the dichotomy between the two cases is illustrative of the potential impact of the *Caronia* decision. Par's complaint requested a declaration that the regulations implementing the misbranding provisions of the FDCA be declared unconstitutional insofar as the FDA's interpretation of those regulations bars truthful and non-misleading speech concerning off-label use of FDA-approved drugs.[96] On the other hand, in its settlement with the government, Amgen pled guilty to a misbranding charge, in which the government alleged that "in order to increase sales of [its] drug and reap the resulting profits, Amgen illegally sold the drug with the intention that it be used at off-label doses *that the FDA had specifically considered and rejected*."[97] Moreover, the civil settlement resolved allegations that Amgen paid illegal kickbacks to spur prescriptions, and that Amgen engaged in "*false* price reporting practices."[98] In this regard, because *Caronia* applies only to *truthful*, *non-misleading* off-label promotion, cases like Amgen – which apparently involved some false and misleading conduct (not to mention allegations of kickbacks) – will likely continue to be prosecuted aggressively. On the other hand, in situations such as the one Par Pharmaceutical finds itself – where arguably only truthful information is at issue – the government's position is significantly weakened, and manufacturers may find the *Caronia* case provides significant leverage in negotiations involving ongoing investigations by the government.

Thus, while *Caronia* may not significantly deter the government from investigating and prosecuting manufacturers for off-label promotion, the case will almost certainly serve to alter the government's strategy and tactics with respect to the way it chooses cases to bring, and with respect to the way it presents those cases in the event they are litigated. First, the *Caronia* decision did not declare the FDCA's misbranding provisions unconstitutional: instead, the Second Circuit held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[99] In so ruling, the *Caronia* court distinguished between truthful and untruthful speech in order to avoid declaring the misbranding provisions unconstitutional:

> [E]ven if speech can be used as evidence of a drug's intended use, we 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. *We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs.*[100]

By construing the FDCA narrowly in order to avoid a ruling on the constitutionality of the FDCA itself, the Second Circuit essentially held that the FDCA's misbranding provisions exempt "truthful off-label promotion," which in turn would indicate that the Second Circuit considers falsity to be an element of the criminal misbranding provisions. If the *Caronia* reasoning is adopted by other courts, and truthful off-label promotion is exempted

96 *See Par Pharmaceutical, Inc. v. United States,* No. 11-cv-1820-RWR, Dkt. No. 1 at pp. 32-33 (D.D.C. Oct. 14, 2011).
97 Amgen Press Release, *supra* note 42 (emphasis added).
98 *Id.* (emphasis added).
99 Caronia, 2012 WL 5992141, at *15.
100 *Id.* (emphasis added).

from the FDCA's misbranding prohibitions, then in future criminal off-label prosecutions the burden would fall to the government to show that the promotional statements at issue were intentionally false or misleading.[101]

In that regard, one should expect to see increased scrutiny by the government of off-label promotion charges. Before bringing a case, the government will ensure there existed strong evidence that a company or its representative made knowing statements about the safety or efficacy of their products that were false, misleading, or omitted critical information. In other words, in future off-label promotion cases, the government is likely to focus on instances where off-label promotional statements are demonstrably false. Manufacturers can expect to see, therefore, the development of a meaningful First Amendment safe harbor for truthful and non-misleading promotional speech. As a corollary, it is unlikely that prosecutors will bring criminal charges against companies for off-label promotion when there is strong scientific support for the off-label promotional statements at issue.[102] Of course, what precisely constitutes strong scientific support, or truthful and non-misleading information, will still be subject to debate.

As previously discussed, prosecutors have been branching out from the traditional sales representative-initiated speech for evidence of off-label promotion. More specifically, there has been a greater focus on the underlying scientific studies and data used to support promotional speech. In the wake of *Caronia*, manufacturers should expect to see even greater focus in these areas. Indeed, in light of *Caronia*, the government will often be required to delve into the clinical data supporting off-label promotional statements in order to determine whether those statements are truthful and non-misleading.

Manufacturers should expect to see continued scrutiny of post-market clinical study design, primary and secondary endpoint analysis, and disclosure (or lack of such) of clinical study results. The science undergirding promotional statements will be carefully evaluated before prosecutors decide to initiate investigations, and will be further evaluated if and when prosecutors levy charges against a manufacturer. In addition, and in light of *Caronia*, the FDA and prosecutors will be forced to articulate more directly what they consider valid and truthful scientific information.

If other courts begin to embrace *Caronia*'s First Amendment reasoning in more cases, the FDA may be forced to issue guidance that would serve to delineate a safe harbor – the type of off-label information the Agency considers truthful and non-misleading. In this regard, a Citizen Petition filed by seven pharmaceutical manufacturers in 2011 could serve as a framework for such guidance. The Citizen Petition notes the uncertainty surrounding the current FDA position on off-label promotion and asks FDA to

---

101 *Cf. United States v. Harkonen*, No. 11-10209 (9th Cir. Mar. 4, 2013), *available at* http://cdn.ca9.uscourts.gov/datastore/memoranda/2013/03/04/11-10209.pdf. In 2009, a jury convicted Scott Harkonen, the former CEO of InterMune, Inc., of wire fraud based on a press release that fraudulently described clinical trial results about the drug Actimune. The district court in the northern district of California sentenced Harkonen to 3 years probation, 6 months home detention, community service, and a $20,000 fine. Both parties appealed to the Ninth Circuit. In a short unpublished opinion, the Ninth Circuit affirmed the district court. Harkonen challenged the conviction arguing that the First Amendment barred his prosecution. The Ninth Circuit applied a two-part analysis: (1) whether sufficient evidence supports the verdict; and (2) if so, whether the facts as found by the jury establish the core constitutional facts. The Ninth Circuit emphasized that the First Amendment does not protect fraudulent speech. Therefore, the court identified the core constitutional issue in Harkonen's case as whether there was sufficient evidence to support the jury's finding that the press release was fraudulent. Deferring to the jury's findings on the elements of the wire fraud charge, the Ninth Circuit affirmed the wire fraud conviction. Importantly, Harkonen was convicted of wire fraud which required a finding that the statements he made were fraudulent. The jury acquitted Harkonen of the misbranding charge, so unlike *Caronia*, the Harkonen case did not present a First Amendment defense based on truthful and non-misleading statements about an unapproved use of a drug. In other words, the jury's finding that Harkonen knowingly participated fraudulent activity distinguishes the Harkonen case from the *Caronia* case and other off-label enforcement actions where there have not been formal findings of fraudulent off-label statements.

102 *See* Sandburg *supra*, note 87.

clarify its position with respect to the following: (1) manufacturer responses to unsolicited requests for off-label information; (2) the meaning of "scientific exchange" and activities that would constitute scientific exchange; (3) interactions with formulary committees, payors, and similar entities; and (4) the dissemination of third-party clinical practice guidelines.[103]

Given the fact that the Supreme Court spoke clearly on the contours of the commercial speech doctrine only two years ago in Sorrell v. IMS Health, Inc., and in light of the FDA's recent setback in *Caronia*, the government may take the opportunity to develop a sensible policy to guide manufacturer conduct regarding off-label promotion. Such a policy would be welcomed by the industry and could ultimately ensure that more relevant and timely scientific information reaches physicians and prescribers.

V. Conclusion

The Second Circuit's *Caronia* decision represents an unmistakable setback to the government's current theory underlying its enforcement of off-label promotion. As confirmed by the *Caronia* court, truthful and non-misleading off-label promotional speech is entitled to First Amendment protection. Manufacturers should seek, and FDA should recognize, a First Amendment safe harbor as the framework surrounding off-label promotion enforcement continues to develop. As discussed above, however, *Caronia* only alters the playing field to some degree. As seen by the government's increased scrutiny of clinical data and the scientific exchange process, the government has many tools and theories still available to combat what it considers to be misleading and untruthful promotional speech. In the wake of *Caronia*, therefore, manufacturers will still need to continue to carefully screen and control their promotional materials.

103 *See* FDA Citizen Petition (Jul. 5, 2011), *available at* www.regulations.gov, Docket No. FDA-2011-P-0512. The Citizen Petition was submitted on behalf of the following companies: Allergan, Inc.; Eli Lilly and Co.; Johnson & Johnson; Novartis Pharmaceuticals Corp.; Novo Nordisk, Inc.; Pfizer, Inc.; and Sanofi-Aventis U.S. LLC.