United States v. Caronia: How True Does "Truthful" Have to Be?

I. OFF-LABEL PROMOTION: HEALTH CARE FRAUD OR PERMISSIBLE SPEECH?

When does promotional speech rise to the level of health care fraud? Prescribing drugs for off-label uses provides lifesaving innovation to many who cannot wait for a drug to go through FDA approval. The practice also invokes similar concerns as the garden-variety health care fraud: overuse, waste, and information asymmetry between patients and providers regarding quality and necessity of care. Physicians' freedom to use drugs off-label stems from the government's refusal to directly regulate the practice; however, without direct regulation, the government has struggled to prevent abuse of this practice. The government traditionally resorted to indirectly regulating promotion of off-label uses by pharmaceutical companies, in order to provide physicians with the best information. *United States v. Caronia*[1] curtails the government's ability to indirectly regulate promotions and further complicates this puzzle.

A drug is used in an "off-label" capacity when the drug is administered for a disease, dosage, or population for which it did not receive approval from the Food and Drug Administration ("FDA").[2]

1. 703 F.3d 149 (2d Cir. 2012).

2. Christopher M. Wittich, et al., *Ten Common Questions (and Their Answers) About Off-Label Drug Use*, 87 MAYO CLINIC PROCEEDINGS 982, 982 (2012).

Physicians are allowed to prescribe drugs off label;[3] however, through various regulations, guidance documents, and consent decrees, the FDA has interpreted manufacturer promotion of off-label drug uses as "misbranding."[4] Section 331 (a)–(c) of the Food, Drug, and Cosmetic Act ("FDCA") prohibits the introduction, receipt, or actual production of "misbranded" drugs in interstate commerce.[5] Sections 333(a)(1) and (2) provide felony and misdemeanor liability for such misbranding violations.[6]

Pharmaceutical companies find off-label uses highly profitable, and they have every incentive to market their drugs for off-label uses, even off-label uses that have not been proven to be safe or effective.[7] Off-label promotion harms consumers when it leads to inappropriate prescriptions. If physicians read and correctly analyze new drug research, and base their prescriptions on current research rather than pharmaceutical promotion, fraudulent off-label promotion might be innocuous. Current research on physician learning patterns, however, is not optimistic; physicians have a hard time keeping up with drug developments and research[8] and often view information provided by

3. 21 U.S.C. § 396 (2012) ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").

4. Thea Cohen, *The First Amendment and the Regulation of Pharmaceutical Marketing: Challenges to the Constitutionality of the FDA's Interpretation of the Food, Drug, and Cosmetics Act*, 49 AM. CRIM. L. REV. 1945, 1947 (2012).

5. 21 U.S.C. § 331 (a)–(c) ("(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded. (b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce. (c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.").

6. 21 U.S.C. § 333 (a) (1)–(2); *see also* United States v. Caronia, 703 F.3d 149, 154 (2d Cir. 2012) ("The consequences for misbranding are criminal.").

7. George S. Craft, Jr., *Promoting Off-Label in Pursuit of Profit: An Examination of A Fraudulent Business Model*, 8 HOUS. J. HEALTH L. & POL'Y 103, 105 (2007) (noting the profitability of off-label uses to pharmaceutical companies and the "self-serving" business model it creates).

8. Dr. Williamson conducted a survey of physicians and found that 87% of practitioners surveyed assure themselves of a study's soundness by comparing the results to their own experience. Only 27% looked at the methods section of a study. John W. Williamson, et al., *Health Science Information Management and Continuing Education of Physicians: A Survey of U.S. Primary Care Practitioners and Their Opinion Leaders*, 110 ANNALS OF INTERNAL MED., Jan. 15, 1989 at 157. *See also* Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J.L. SCI. & TECH. 61, 76 (2008) (noting that physicians may be influenced by anecdotal case studies as much as rigorous scientific studies and that they value the experiences of their peers as much or more than rigorous studies).

pharmaceutical representatives as useful and accurate.[9] Consequently, fraudulent off-label promotion is likely to lead to medically unnecessary or unsafe off-label prescriptions and invokes the same concerns of overuse, waste, and information asymmetry as traditional health care fraud.

The FDA has historically pursued off-label promotions involving intentionally false or misleading statements.[10] Recent enforcement suggests that the FDA has broadened its net. The FDA recognizes that exceptions to its formal approval process can benefit society but also perceives the potential for interested actors to exploit those exceptions.[11] To balance these two considerations, the FDA periodically attempts to regulate drug regimes informally through restrictions on promotion.[12]

United States v. Caronia[13] challenged the FDA's position that ostensibly "truthful" off-label promotion alone could constitute a misbranding violation. Alfred Caronia was hired by Orphan Pharmaceutical in 2005 as a Specialty Sales consultant to promote Xyrem, a sleep-inducing depressant approved to treat cataplexy and excessive daytime sleepiness.[14] In the spring of 2005, the federal government launched an investigation of Orphan for promoting Xyrem's off-label uses;[15] during this investigation, the government recorded Mr. Caronia promoting Xyrem for off-label uses to a physician posing as a potential Xyrem customer.[16]

The government charged Mr. Caronia with misdemeanor misbranding;[17] though Mr. Caronia moved to dismiss the charges, the Eastern District of New York dismissed his motion.[18] Mr. Caronia was sentenced to one year of probation, one hundred hours of community

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9. THE KAISER FAMILY FOUNDATION. NATIONAL SURVEY OF PHYSICIANS PART II: DOCTORS AND PRESCRIPTION DRUGS 5 (2002), *available at* http://www.wcl.american.edu/pijip/documents/Kaiser-March2002.pdf

10. "A Deep Dive Into the Second Circuit's *Caronia* Decision, Potential Next Steps, and Potential Enforcement Fallout." FDA LAW BLOG: THE OFFICIAL BLOG OF HYMAN, PHELPS & MCNAMARA. (December 12, 2012), *available at* http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/12/a-deep-dive-into-the-second-circuits-caronia-decision-potential-next-steps-and-potential-enforcement.html.

11. Thompson v. W. States Med. Ctr., 535 U.S. 357, 379 (2002) (Breyer, J., dissenting) (explaining the balancing of the FDA's interest in providing compounded drugs to those who need them but "confin[ing] the sale of untested, compounded, drugs to where they are medically needed.").

12. *See infra* Part III.

13. *Caronia*, 703 F.3d at 152 (2d Cir. 2012).

14. *Id.* at 155–56.

15. *Id.*

16. *Id.*

17. *Id.* at 157.

18. *Id.* at 158.

service, and a $25 special assessment.[19] Mr. Caronia appealed, arguing that the FDCA's misbranding provisions unconstitutionally restrict speech when applied to a truthful, nonmisleading off-label use.[20] The Second Circuit agreed, reversing his conviction.[21]

The Second Circuit's opinion in *Caronia* could be dismissed as a fluke reaction to the prosecution's emphasis on speech, as the prosecution mentioned Mr. Caronia's off-label promotion over forty times at trial.[22] The Second Circuit's reversal, however, is consistent with the historical trend limiting the FDA's ability to regulate drug regimes by restricting promotional speech. The court correctly extended prior precedent on FDA's indirect drug regulation to avoid punishing "truthful" conduct with a criminal sanction.

Despite the correct outcome, the Second Circuit's decision glosses over real concerns about extending First Amendment protection to ostensibly truthful off-label promotion. Part II provides context to the Second Circuit's decision by tracing the historical trend of courts awarding pharmaceutical companies greater commercial speech protection. Given current case law, Part III.A argues that *Caronia* extends this trend to "truthful" promotion. Part III.B discusses two different standards of "truthfulness" envisioned by courts, and Part III.C explores the danger of conflating these two standards, given the realities of the current health care information system. The Comment concludes that, despite real concerns about using a broad standard of truthfulness, the Second Circuit correctly declined to enforce such a stringent standard of truthfulness using a criminal sanction. Part IV concludes.

II. LIBERALIZATION OF COMMERCIAL FREE SPEECH FOR DRUG PROMOTION

The FDA has long battled with the courts over the boundary between protected commercial speech and its ability to indirectly regulate flexible drug regimes. Historically, the FDA freely limited through speech restrictions drug practices exempted from its formal drug approval process.[23] In recent years, however, courts have restricted this power. The *Washington Legal Foundation* ("*WLF*")

19. *Id.* at 159–60.

20. *Id.* at 160.

21. *Id.* at 169.

22. *Id.* at 161.

23. *See* United States v. Caputo, 517 F.3d 935, 938 (7th Cir. 2008) (explaining that the defendant's argument would have been laughable only thirty years prior).

cases began this shift.[24] The Washington Legal Foundation claimed that FDA guidance limiting the type of journal article reprints and scientific publications that manufactures could distribute to providers regarding off-label uses violated the First Amendment.[25] The district court analyzed the guidance under the *Central Hudson*[26] test for commercial speech and found that the guidance was more extensive than necessary to advance the government's substantial interest.[27]

Concerned about the constitutionality of the pending Food and Drug Administration Modernization Act of 1997 ("FDAMA"), which contained many similar restrictions,[28] the FDA moved that the court confine its injunction to the Guidance.[29] Instead, the district court further held that the new FDAMA provisions would also be unconstitutional.[30] The FDA initially appealed;[31] however, upon appeal, the FDA explained that the new provisions acted as safe harbors rather than substantive regulations.[32] The appellate court seemed to suspect that the FDA simply did not want the provisions

24. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998), *amended*, 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed, judgment vacated in part sub nom.* Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000), *and amended*, 36 F. Supp. 2d 418 (D.D.C. 1999), *and appeal dismissed, judgment vacated in part sub nom.* Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

25. Washington Legal Found. v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000). The requirements for unsolicited distribution of scientific texts included that "the work may not have been written, edited, excerpted or published specifically at the request of a drug, device or biologic firm, unless the text was prepared in a manner that results in a balanced presentation; the content may not have been reviewed, edited or significantly influenced by the manufacturer; the text should not be available primarily through the manufacturer—it should be generally available in other outlets such as bookstores . . ."; Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 58 (D.D.C. 1998).

26. The *Central Hudson* test outlines the requirements for commercial free speech protection and consists of four prongs: 1) the speech must not be misleading and concern lawful activity, 2) the asserted government interest is "substantial," 3) the regulation "directly advances" the asserted governmental interest, and 4) the regulation is "narrowly drawn," and is not broader than necessary to address the stated interest. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York, 447 U.S. 557, 566 (1980).

27. Washington Legal Found. v. Henney, 202 F.3d 331, 334 (D.C. Cir. 2000).

28. *Id.* (requiring that manufacturers must file supplemental approval for off-label use, send materials to the FDA before distribution, materials should not be abridged, must state that the use is unapproved, and other information "necessary to provide objectivity and balance").

29. *Id.*

30. Washington Legal Found. v. Henney, 56 F. Supp. 2d 81, 87 (D.D.C. 1999), *appeal dismissed, judgment vacated in part*, 202 F.3d 331 (D.C. Cir. 2000). Interestingly, the court noted that in lieu of these more strenuous restrictions, the FDA was able to restrict off-label promotion in some way, in order to incentivize formal FDA approval. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998).

31. Washington Legal Found. v. Henney, 202 F.3d 331, 334–35 (D.C. Cir. 2000).

32. *Id.* at 335–36.

explicitly struck down;[33] however, given the changed position, the court found the issue to be moot and dismissed the case.[34]

Two years later, in a case about drug-compounding pharmacies, the Supreme Court further liberalized commercial speech for drug promotion. In *Thompson v. Western States Medical Center*, the Supreme Court paved the way for the Second Circuit's decision in *Caronia*, ruling that FDAMA provisions restricting compounding pharmacies' promotion of drugs violated commercial free speech.[35] Drug-compounding units are allowed to custom mix drugs for people with particular allergies or special needs without FDA approval.[36] The goals underlying both drug-compounding pharmacies and off-label drug use are very similar: both practices provide alternative procedures for drug delivery to previously undertreated populations, but both must protect against the alternative procedures undermining the formal drug approval process.

Western States more closely scrutinized the third and fourth prongs of the *Central Hudson* test for commercial free speech than even the *WLF* court and issued an opinion that the Second Circuit echoed in *Caronia*. *Western States* relied heavily on the "truthfulness" of the compounded drug advertisements and on physicians' expertise to suggest that the regulation did not "directly advance" the government's goal,[37] rationales the Second Circuit also articulated in *Caronia*.[38] *Western States* similarly suggested a litany of alternative volume- and equipment-based restrictions as evidence that the speech regulation was not "narrowly drawn,"[39] a tactic also used by the Second Circuit.[40] When the Court struck down the promotion restrictions, the FDA relegated itself to scrutinizing drug compounding pharmacies' promotions for false or misleading statements through warning letters.[41]

Not all cases involving promotion restrictions under the FDCA are in line with this trend toward greater commercial speech;

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33. *See id.* at 335 (noting that the dispute has "disappeared before our eyes" and that the parties' briefs were "quite confusing").

34. *Id.* at 336–37.

35. Thompson v. W. States Med. Ctr., 535 U.S. 357, 360 (2002).

36. *Id.* at 361.

37. *Id.* at 368–377.

38. *Caronia*, 703 F.3d at 166–67.

39. Thompson v. W. States Med. Ctr., 535 U.S. 357, 371–73 (2002).

40. *Caronia*, 703 F.3d at 167–68.

41. Jonathan J. Darrow, *Pharmacy Compounding: Federal Law in Brief*. BILL OF HEALTH, HARVARD LAW (Nov. 1, 2012), *available at* http://blogs.law.harvard.edu/billofhealth/2012/11/01/pharmacy-compounding-federal-law-in-brief/ (citing http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048441.htm).

however, upon appeal, the initial rationales of these district court holdings are often called into question. In *United States v. Caputo*, defendants were charged with introducing an adulterated or misbranded device into interstate commerce by promoting it for uses that were not FDA approved.[42] The court in *Caputo* noted that promotion restrictions "directly advanced" the substantial interest of preserving the FDA approval process because promotion restrictions were "one of the few mechanisms available to the FDA to compel manufacturer behavior . . ."[43] The court drew on *WLF*, which—despite finding the speech restrictions too onerous—had anticipated some level of acceptable promotion restrictions, noting "that permitting Defendants to engage in all forms of truthful, non-misleading promotion of off-label use would severely frustrate the FDA's ability to evaluate the effectiveness of off-label uses."[44] The district court also did not see a less burdensome way to advance the FDA's interest.[45]

Upon appeal, the Seventh Circuit noted that, given the Supreme Court's guidance in *Western States*, it may have reversed the First Amendment decision if it had been raised.[46] The Seventh Circuit acknowledged the difficulty of sorting through this issue: it weighed the costs of imposing speech restrictions against the possible perverse consequences of broadening commercial free speech (e.g., the danger that the FDA will be less likely to approve a drug in case the drug has questionable additional uses).[47] The Seventh Circuit concluded that it was glad it was not bound to decide this question yet.[48]

Four years later, the Second Circuit directly faced the question the *Caputo* court willingly dodged. Given the trend towards greater commercial free speech in drug regulation, however, the *Caronia* decision seems foreseeable. Caronia's ostensibly "truthful" promotion made courts unwilling to impose criminal sanctions.

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42. United States v. Caputo, 288 F. Supp. 2d 912, 914 (N.D. Ill. 2003).

43. *Id.* at 921 (quoting Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998)).

44. *Id.* at 921–22.

45. *Id.*

46. United States v. Caputo, 517 F.3d 935, 939–40 (7th Cir. 2008).

47. *Id.*

48. *Id.*

III. ARGUING AROUND THE TRUTH

A. The Second Circuit Finds the Restriction of "Truthful" Speech Unconstitutional

In analyzing the constitutionality of the FDCA's alleged speech restrictions, the Second Circuit noted the speech should be subject to heightened scrutiny because of its content- and speaker-based restrictions, as noted in *Sorrell v. IMS Health Inc.*[49] However, the court actually applied the *Central Hudson* test, apparently because the heightened test was ill-established.[50]

The Second Circuit found that the first two prongs of the *Central Hudson* test were satisfied. First, the court held that Caronia's speech concerned lawful activity and was not inherently misleading.[51] Second, the Second Circuit found that the government has a substantial interest in restricting manufacturer promotion of off-label uses, namely preserving the FDA drug approval process and steering off-label uses toward the formal approval process.[52]

The Second Circuit, however, found that the restriction violated the third and fourth prongs of the *Central Hudson* test. The regulation violated the third prong for two reasons: First, since the FDA approval process already anticipates off-label use, off-label promotion cannot interfere with the integrity of the FDA's drug approval process.[53] Second, such a regulation would be "paternalistic" and could inhibit beneficial learning about "truthful and nonmisleading scientific and medical information" on off-label uses.[54] Though the court acknowledged that some off-label information could be misleading, it noted that this case did not involve misleading information.[55]

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49. *Caronia*, 703 F.3d at 163–64. This Comment will not focus on the *Sorrell* decision in depth since the decision did not regulate drug promotion but rather the sale of "prescriber-identifying information." Sorrell v. IMS Health Inc., 131 S.Ct. 2653, 2659 (2011).

50. Marc J. Scheineson & Guillermo Cuevas, United States v. Caronia, *the Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion As "False and Misleading"*, 68 FOOD & DRUG L.J. 201, 210 (2013).

51. *Caronia*, 703 F.3d 149, 165–66 (2d Cir. 2012); United States v. Caronia, 576 F. Supp. 2d 385, 397 (E.D.N.Y. 2008).

52. *Caronia*, 703 F.3d at 166; Caronia, 576 F. Supp. 2d at 398 (citing Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002)).

53. *Caronia*, 703 F.3d at 166–67.

54. *Id.* (citing *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, DEP'T OF HEALTH AND HUMAN SERV. (Jan. 2009), *available at* http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm).

55. *Id.*

The Second Circuit rejected the fourth prong because it found several less burdensome alternatives to regulating off-label promotion "without excessive First Amendment restrictions."[56] The Second Circuit mirrored the *Western States*' list of alternatives, although these alternatives might seem less applicable to off-label prescriptions than to drug-compounding production.[57] The court rejected as conclusory the government's defense that the alternatives are "not administrable, feasible, or otherwise effective."[58] Since the third and fourth prongs of the *Central Hudson* test were violated, the Second Circuit vacated the judgment and remanded the case back to the district court.[59]

In the aftermath of the ruling, the FDA announced that it would not appeal the decision because it did not think the decision would "significantly affect the agency's enforcement."[60] However, despite the FDA's optimism, this ruling clarified a previously nebulous boundary on the FDA's ability to informally regulate off-label drug regimes.

B. Using "Truth" as a Shield

The Second Circuit premised a lot of its *Central Hudson* analysis, particularly the analysis of the third prong, on the perceived truthfulness of the promotion. The court used the "truthful" nature of the promotion to hold that in this context the regulation does not "directly advance[]" a substantial government goal in two ways.[61]

First, the court noted that since the current approval regime does not prohibit off-label drug use, restriction of "truthful" promotion cannot further the government's goals of preserving the current approval regime.[62] Since the government interest is to preserve the current approval regime, and the current approval regime already allows for off-label drug prescriptions, restricting information that aids in off-label prescriptions could not promote the government's interest.

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56. *Id.* at 167.

57. Among these would be to 1) provide guidance in differentiating between misleading and truthful information, 2) create warning systems or safety tiers for off-label uses of drugs, 3) "require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval," and 4) impose volume-based limits on off-label drugs. *Id.* at 168.

58. *Id.*

59. *Id.* at 169.

60. Scheineson & Cuevas, *supra* note 50, at 211–12.

61. *Caronia*, 703 F.3d 149, 166–67.

62. *Id.* at 166 (emphasis added).

Second, the "truthful" nature of the speech leads to accusations of paternalism. Indeed, in assessing whether the regulation directly advances the substantial goal, the courts in *Caronia* and *Western States* quoted *44 Liquormart, Inc. v. Rhode Island,* saying that regulations banning truthful, nonmisleading commercial speech "usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth."[63] These courts seemed to suggest that the only danger that could come from "truthful" information would be due to an irrational or unexpected response. They saw "truth" as a dichotomous concept and assumed "truthful" information could never mislead a rational person.

The definition of "truthful" here, however, is unclear. Courts have come up with at least two different standards of truthfulness. The Second Circuit seemed to define truthfulness as the absence of blatantly false or misleading statements.[64] The dissent noted that the majority allows "merely unsubstantiated, rather than *demonstrably* false or misleading" statements.[65]

The *Western States* dissent identified a second standard. In response to the majority's accusations of paternalism in restricting speech, Justice Breyer's dissent emphasized that his concern is the lack of *complete* information, "of advertisements that will not fully explain the complicated risks at issue."[66] This standard of "truthfulness" is more restrictive than that of the *Caronia* or *Western States* majorities.

Notably, these standards of "truthfulness" are actually a combination of two separate considerations: whether the speech is truthful and whether it is nonmisleading. Although these components are separable,[67] the dividing line between them can be blurry in practice. One way to understand the Second Circuit's standard is that it imposes a presumption of truthfulness, rather than of falsity. Indeed, the dissent suggests that the majority requires the

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63. Thompson v. W. States Med. Ctr., 535 U.S. 357, 375 (2002) (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996)); United States v. Caronia, 703 F.3d 149, 166 (2d Cir. 2012) (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996)).

64. The court equates Caronia's "truthful" promotion with the fact that "this case does not involve false or misleading promotion." *Caronia*, 703 F.3d at166–67.

65. *Caronia*, 703 F.3d at 178 (Livingston, J., dissenting) (emphasis added).

66. Thompson v. W. States Med. Ctr., 535 U.S. 357, 387 (2002) (Breyer, J., dissenting).

67. For a discussion of the difference between false and misleading speech from an epistemological perspective, see Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment.* 94 BOSTON UNIV. L. REV. 545, 568 (2014).

government to bear the burden of demonstrating falsity.[68] Dr. Christopher Robertson critiques the Second Circuit's presumption of truthfulness regarding the safety and efficacy of a drug, given that the opposite presumption is imposed by the FDA regulatory system, the rules of evidence, and the norms of the scientific community.[69]

The Second Circuit's standard can also be seen as allowing potentially misleading promotion. Speech can be categorized by its likelihood of misleading: "Inherently misleading" speech, speech that is "more likely to deceive the public than to inform it,"[70] is not subject to First Amendment protection.[71] In contrast, speech that is merely "potentially misleading" might still be subject to First Amendment protection.[72] The standard used by the *Western States* majority seemed to allow the latter, as it did not require *complete* information and incomplete information can be potentially misleading.[73] Justice Breyer's dissent, on the other hand, can be seen as denying First Amendment protection to potentially misleading material.[74] In rejecting the narrow standard of truthfulness, the Second Circuit refuses to sanction potentially misleading promotions and imposes a presumption of truthfulness.

C. How True Does "Truthful" Have To Be?

To understand the ramifications of the Second Circuit's choice of truthfulness standard, it must be examined with respect to the realities of the health care information system. The court's choice of the broad "truthfulness" standard can seem problematic, given pharmaceutical companies' demonstrated ability to "manipulat[e] the information marketplace."[75] "Gag clauses" contractually prevent clinical investigators from publishing unfavorable results.[76] Similarly,

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68. *Caronia*, 703 F.3d at 178 (Livingston, J., dissenting). Notably, although Caronia claimed Xyrem was a safe drug on both recorded meetings, Xyrem did have significant risks associated with its use, as it received a black box warning from the FDA. *Id.* at 172 n.3.

69. Robertson, *supra* note 67, at 571.

70. Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 66–67 (D.D.C. 1998) (citing Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of New York, 447 U.S. 557, 563 (1980) (citations omitted)).

71. Scheineson & Cuevas, *supra* note 50, at 212.

72. *Id.*

73. Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002). Some scholars have wondered how much authority the FDA has to proactively classify speech as misleading. Scheineson & Cuevas, *supra* note 50, at 211–14.

74. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 387 (2002) (Breyer, J., dissenting) (discussing the dangers of "not fully explain[ing] the complicated risks at issue.").

75. Fazal Khan, M.D., J.D. & Justin Holloway, J.D., *Verify, Then Trust: How to Legalize Off-Label Drug Marketing*, 117 PENN ST. L. REV. 407, 412–13 (2012).

76. *Id.* at 421.

publication bias results when published results are not representative of the whole body of actual results, generally in a way that favors the pharmaceutical company.[77] There are many types of publication bias: "selected outcome bias" occurs when primary and secondary outcomes are selectively chosen based on the study's results,[78] and "location bias" refers to the practice of publishing a negative result in a lower circulating journal.[79] These possibilities are not hypothetical—Kaiser brought Racketeer Influenced and Corrupt Organizations Act charges against Pfizer for these marketing practices in promoting off-label uses of Neurontin.[80] This sort of manipulation would be difficult to catch even by a highly trained medical professional, undermining the idea that restrictions are unduly paternalistic. Even cherry-picking published studies to share with a doctor can present a "potentially misleading" message. While a recent case suggests that publicizing overoptimistic conclusions from a study does not automatically qualify for First Amendment protection,[81] more subtle forms of publication bias might. Indeed, the restrictions struck down in *WLF*[82] sought to require pharmaceutical companies to distribute representative results. The Second Circuit's standard, in short, seems to allow promotion that is not blatantly false or inherently misleading but presents nonrepresentative results using tactics that are difficult for medical professionals to detect.

Requiring "complete truthfulness," on the other hand, might be too rigorous a requirement to impose *indirectly*. "Complete truthfulness" resembles the standard to which the FDA subjects its approved drugs, the standard with which it *directly* regulates.[83] The FDA drug approval process involves a team comprised of medical doctors, microbiologists, pharmacologists, chemists, statisticians, and other experts, who "analyze[] study results and look[] for possible issues with the application, such as weaknesses of the study design or analyses."[84] Reviewers exhaustively vet the results and conclusions

77. In re Neurontin Mktg. & Sales Practices Litig., No. 04 -10739-PBS, 2011 WL 3852254 at *8 (D. Mass. Aug. 31, 2011), *aff'd*, 712 F.3d 21 (1st Cir. 2013).

78. *Id.*

79. *Id.*

80. *Id.* Notably, the court found that Pfizer engaged in actively suppressing negative results in addition to these other forms of publication bias, making it unclear whether these biases alone would rise to the level of false or misleading. *Id.* at *2.

81. United States v. Harkonen, No. 08-00164, 2009 WL 1578712 at *6 (N.D. Cal. June 4, 2009).

82. *See* supra note 25.

83. *See* FDA's Drug Review Process: Continued. FDA. (March 13, 2012) *available at* http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm.

84. *Id.*

and decide whether they need more information before making an approval decision.[85]

Given the rigorous standard the FDA wants to impose, and the criminal sanction used to enforce the standard, the Second Circuit's choice to adopt the broader standard of truthfulness was fair. The FDA prefers an almost-categorical ban on off-label promotion based on the overwhelming likelihood that the "truthful" speech will not reach its level of "complete truthfulness." As the Seventh Circuit noted in *Caputo*, the Supreme Court wants the FDA to either substantively regulate off-label use (by explicitly subjecting them to such rigorous approval process) or to place the burden of warning physicians on themselves.[86] It appears disingenuous to indirectly require from pharmaceutical manufacturers the same level of truth explicitly required through the formal approval process, while claiming not to regulate off-label uses of drugs.[87] It seems especially unfair to police this requirement with a criminal sanction; the Second Circuit noted that the First Amendment claim is "more compelling" here because of the criminal sanction.[88]

Explicitly distinguishing between the standards of truthfulness, however, is critical. The presumption of truthfulness does not prove actual truthfulness, and potentially misleading speech is not the same as truthful speech. The Second Circuit's broad standard of truthfulness is not rigorous enough to support its claims that the FDA's efforts to restrict information are counterproductive or paternalistic.[89] There is real danger from allowing potentially misleading promotion. Given the severity of the punishment, however, this danger might be better pursued under a different sanction.

IV. THE FUTURE OF "TRUTHFUL" OFF-LABEL PROMOTION

The Second Circuit's treatment of off-label promotion in *Caronia* was not an idiosyncratic reaction to a particularly aggressive government prosecution. Instead, the opinion fits with the judicial trend limiting the FDA's ability to regulate drugs through speech

85. *Id.*

86. United States v. Caputo, 517 F.3d 935, 939 (7th Cir. 2008).

87. *See also* Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 340 (2011) (noting that the government "cannot achieve its regulatory goal furtively through suppression of information and opinion").

88. *Caronia*, 703 F.3d at 165. The dissent also hypothesized that the outcome was driven by the fact that "[a]t bottom, the majority is troubled that 'the simple promotion of a drug's off-label use' can lead to criminal liability under the FDCA." *Id.* at 174 (Livingston, J., dissenting).

89. *Caronia*, 703 F.3d 149, 166 (2d Cir. 2012) (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996)).

restrictions rather than through substantive regulation. While imposing a more restrictive standard of truthfulness in order to qualify for First Amendment protection might be attractive, imposing it indirectly with a criminal sanction seems unduly harsh and not consistent with other jurisprudence. Instead, a civil sanction might be preferable. Alternatively, imposing a less restrictive version of the FDAMA guidelines to combat publication bias or instituting a presumption of falsity at trial[90] could also address this issue.

Although scholars have suggested that the Supreme Court might review the constitutionality of truthful off-label promotion in the future,[91] the FDA will likely avoid higher review. The FDA has decided not to appeal in this case.[92] The FDA seems more likely to shy away from final rulings on its ability to indirectly regulate drugs (as it did in *WLF*)[93] and instead informally police through warning letters or safe harbors, (as it did after *Western States*).[94] However, given the growing health care industry, society must eventually decide if ostensibly truthful off-label promotions by self-interested companies constitute a high enough probability of waste and overuse to explore a constitutional avenue for regulating pharmaceutical manufacturer speech.

Elissa Philip[*]

90. For an exploration of this solution, see Robertson, *supra* note 67, at 574.

91. Allen Rostron, *Pragmatism, Paternalism, and the Constitutional Protection of Commercial Speech*, 37 VT. L. REV. 527, 562 (2013)).

92. Scheineson & Cuevas, *supra* note 50, at 211–12.

93. Washington Legal Found. v. Henney, 202 F.3d 331, 335–36 (D.C. Cir. 2000).

94. Jonathan J. Darrow, *Pharmacy Compounding: Federal Law in Brief*. BILL OF HEALTH, HARVARD LAW (Nov. 1, 2012), *available at* http://blogs.law.harvard.edu/billofhealth/2012/11/01/pharmacy-compounding-federal-law-in-brief/ (citing http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048441.htm).

[*] Vanderbilt University Law School, Doctor of Philosophy Student in Law and Economics and Candidate for Doctor of Jurisprudence, May 2016. I am grateful to Professors Matthew Curley and Brian Roark for providing invaluable feedback. I thank the members of Vanderbilt Law Review *En Banc* for their helpful comments and support throughout the editorial process. All errors remain my own.