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WHEN CLAIMS ABOUT LOLLIPOPS ARE BEST KEPT UNDER WRAPS: CAN THE FDA REGULATE OFF-LABEL SPEECH?

*Emily Moss**

While the COVID-19 pandemic continues, it can be easy to forget other health crises which our country faces. One such crisis is the opioid epidemic. Perhaps unlike the COVID-19 pandemic, “[i]t is accurate to describe the opioid epidemic as a man-made plague, twenty years in the making.”¹ One of its causes was drug manufacturers encouraging doctors to prescribe strong opioids for uses not approved by the FDA.² Such uses are referred to as “off-label” uses.³ For example, one drug manufacturer, Cephalon, promoted an extremely strong opioid, Actiq.⁴ The FDA approved Actiq, a fentanyl product which is consumed in lollipop form for rapid absorption, only for opioid-tolerant cancer patients: “[Actiq] is an opioid analgesic indicated only for management of breakthrough cancer pain in patients 16 and older with malignancies who are *already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.*”⁵ Yet Cephalon and its sales force promoted Actiq to prescribers for unapproved situations, such as migraines,⁶ despite knowledge that the drug could cause “addiction, hypoventilation,

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1. In re Nat’l Prescription Opiate Litig., No. 1:17-MD-2804, 2018 WL 6628898, at *21 (N.D. Ohio Dec. 19, 2018).

2. See 60 Minutes, *Pharma Execs Used Strip Clubs, Broke FDA Law to Boost Opioid Sales*, YOUTUBE (June 23, 2020), https://www.youtube.com/watch?v=G1jLVP156_E.

3. *Id.*

4. *Id.*

5. U.S. Food & Drug Admin., Highlights of Prescribing Information 1 (2007) [hereinafter FDA’s Actiq Label] (emphasis in original).

6. U.S. Dep’t of Justice, *Biopharmaceutical Company, Cephalon, to Pay \$425 Million & Enter Plea to Resolve Allegations of Off-Label Marketing*, JUSTICE.GOV (Sept. 29, 2008), <https://www.justice.gov/archive/opa/pr/2008/September/08-civ-860.html>.

or death, particularly in patients who were not already opioid-tolerant.”⁷

The FDA has long maintained that such off-label promotion is illegal—indeed criminal—regardless of its truth.⁸ Thus, when it discovered Cephalon’s conduct, the government charged Cephalon with off-label promotion. In 2008, Cephalon entered a plea agreement, agreeing to a fine of \$50 million for the off-label promotion of Actiq and two other drugs.⁹

The FDA’s mission is to “protect[] the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation’s food supply, cosmetics, and products that emit radiation.”¹⁰ Due to the increasingly complicated nature of pharmaceuticals,¹¹ the public relies on the FDA to regulate manufacturers’ claims. But current law is expanding First Amendment protection over commercial speech, frustrating the FDA’s important goals.¹² Off-label promotion bans regulate what drug manufacturers can say, and so have met a number of First Amendment challenges.¹³ The FDA off-label promotion ban regulates commercial speech, which must only meet intermediate scrutiny under the *Central Hudson* test.¹⁴ Yet, First Amendment protection of commercial speech has continually expanded.¹⁵ Most recently, the Sixth Circuit held that any content-based restrictions must meet strict scrutiny, even when restricting commercial speech.¹⁶

7. Complaint with Jury Demand at ¶ 15, *Friel v. Cephalon, Inc.*, No. 2:10-CV-00180, (E.D. La. Jan. 27, 2010), ECF No. 1, 2010 WL 1608294 (quoting an indictment charging Cephalon with unlawfully promoting Actiq for non-cancer pain uses not approved by the FDA in violation of 21 U.S.C. § 352(f)).

8. See 21 U.S.C. § 331(a); 21 U.S.C. § 352(f); 21 C.F.R. § 201.5.

9. U.S. Dep’t of Justice, *Pharmaceutical Company Cephalon to Pay \$425 Million For Off-Label Drug Marketing*, JUSTICE.GOV (Sept. 29, 2008), <https://www.justice.gov/sites/default/files/civil/legacy/2014/01/09/Cephalon%20Press%20Release.pdf>.

10. U.S. Food & Drug Admin., *What We Do*, FDA.GOV (March 28, 2018), <https://www.fda.gov/about-fda/what-we-do>.

11. See Philip E. Alford, *Rethinking FDA Regulation of Complex Products*, 21 MINN. J.L. SCI. & TECH. 477, 477–78 (2020).

12. See *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

13. See, e.g., *id.*

14. See *id.* at 164–66.

15. See, e.g., *Int’l Outdoor, Inc. v. City of Troy*, 974 F.3d 690 (6th Cir. 2020).

16. *Id.* at 703.

This Note examines the continually expanding First Amendment protection of commercial speech and its implications on the FDA's off-label promotion ban. Part I provides background on the First Amendment, commercial speech, and how these laws have affected the FDA's off-label promotion ban. Part II explains that the off-label promotion ban is essential to the FDA's important role in protecting the public's health and safety in light of the opioid epidemic—among other concerns. This Note concludes by analyzing possible solutions to First Amendment challenges to the ban.

I. BACKGROUND

A. FDA REGULATION AND OFF-LABEL USE

The Food, Drug, and Cosmetic Act (FDCA) grants the Food and Drug Administration (FDA) the authority to regulate pharmaceutical drugs and medical devices.¹⁷ Through its “notoriously expensive” premarket approval process, the FDA determines if a drug or device is safe and effective for its intended use.¹⁸ A key part of the FDA's approval process is creating a drug label, which outlines the drug's specific approved doses, its targeted diseases, and its intended patients.¹⁹

Once the FDA approves a drug or device for a particular use, physicians may prescribe it for other, off-label uses.²⁰ Off-label prescribing is very common,²¹ accounting for approximately 21%

17. See 21 U.S.C. §301 *et seq.*

18. Carl Wiersum, *No Longer Business as Usual: FDA Exceptionalism, Commercial Speech, and the First Amendment*, 73 FOOD & DRUG L.J. 486, 540 (2018).

19. Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints*, 8 PLOS MED. 1, 9 (2011).

20. Wiersum, *supra* note 18, at 541; *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012).

21. Stephanie M. Greene, *After Caronia: First Amendment Concerns in Off-Label Promotion*, 51 SAN DIEGO L. REV. 645, 648 (2014) (“[O]ff-label marketing has been described as so common among drug and device makers that it’s often dismissed as the equivalent of driving slightly over the speed limit.” (internal quotation marks omitted)); see also Kevin Costello & Eric Johnston, *Manufacturer Liability for Off-Label Uses of Medical Devices*, L.A. LAW., Apr. 2008, at 18 (“[I]t is relatively common for doctors to prescribe drugs or medical devices for off-label uses.”).

of prescriptions in the United States.²² Such off-label prescribing often offers a potential remedy for novel conditions, diseases for which there is no current FDA-approved treatment, medical situations closely related to the drug's approved use, and for patients for whom FDA-approved treatments have failed.²³ The FDA recognizes that off-label "uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature."²⁴

Despite the prevalence and overall acceptance of off-label prescribing, the FDA prohibits manufacturers from promoting off-label uses.²⁵ Manufacturers often market their drugs' on-label uses through a process called "detailing," a common practice where marketers visit doctors in their offices to provide information about the manufacturer's drugs.²⁶ These "detailers" attempt to persuade doctors to prescribe their drugs by providing samples, giving pamphlets, and describing medical studies.²⁷

However, the detailer cannot mention or describe off-label uses. Although the FDCA does not expressly prohibit manufacturer promotion of off-label uses,²⁸ the FDA has stated that "[a]n approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'"²⁹ Misbranding is prohibited under the FDCA.³⁰

22. Shariful A. Syed et al., *The Law and Practice of Off-Label Prescribing and Physician Promotion*, 49 J. AM. ACAD. PSYCHIATRY L. 53, 53–54 (2020).

23. Chelsea Weidman Burke, *The Common, Yet Unspoken, Practice of Off-Label Drug Prescribing*, BIOSPACE (July 1, 2019), <https://www.biospace.com/article/the-common-yet-unspoken-practice-of-off-label-drug-prescribing/>.

24. 12 FDA Drug Bull. 1, 5 (1982).

25. See 21 U.S.C. § 331(a); 21 U.S.C. § 352(f); 21 C.F.R. § 201.5.

26. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557–58 (2011).

27. *Id.*

28. See *United States v. Caronia*, 703 F.3d 149, 154–55 (2d Cir. 2012).

29. U.S. Food and Drug Admin., *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*, FDA.GOV (Jan. 2009), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-reprint-practices-distribution-medical-journal-articles-and-medical-or-scientific-reference>; see also *Caronia*, 703 F.3d at 155.

30. 21 U.S.C. § 331(a) (prohibiting "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded").

Under FDA regulations, manufacturers can communicate about their drugs' off-label uses in at least two ways.³¹ First, they can "respond to unsolicited questions from healthcare professionals about off-label uses."³² "Second, they can disseminate reprints of scientific or medical journal articles or reference books discussing off-label uses of drugs and devices under certain circumstances."³³

Off-label promotion is common, despite the FDA's ban.³⁴ Manufacturers seek to expand use of their drugs to unapproved diseases (the most common goal according to one study), to unapproved subtypes (for example, recommending a drug approved for adults for use in children), and to approved uses at higher than approved doses.³⁵ According to one survey of unsealed whistleblower reports, off-label promotion most often occurs when manufacturers present data of off-label uses to prescribers: "off-label use was frequently encouraged through self-serving presentations of the scientific literature through which physicians were given false or unbalanced study data supporting the unapproved use."³⁶ The FDA can, through a federal prosecutor, criminally charge defendants with misbranding under 21 U.S.C. § 333(a).³⁷ For example, William Facticeau, former CEO of medical device manufacturer Acclarent, was convicted of a federal

31. *Recent Case, First Amendment—Commercial Speech—Second Circuit Holds That Prohibiting Truthful Off-Label Promotion of FDA-Approved Drugs by Pharmaceutical Representatives Violates First Amendment—United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), 127 HARV. L. REV. 795, 801 n.63 (2013) [hereinafter *Recent Case*, HARV. L. REV.].

32. *Id.*; 21 C.F.R. § 99.1 (2013).

33. *Recent Case*, HARV. L. REV., *supra* note 31, at 801 n. 63.

34. Kesselheim, *supra* note 19, at 9.

35. *Id.* at 5.

36. *Id.* ("A common example was selective presentation of favorable studies, where dangers from the off-label uses allegedly being promoted were not mentioned. Other examples included presenting one drug as being superior to another when no head-to-head studies had been conducted and characterizing reports of individual cases or poorly designed studies as definitive evidence supporting an off-label use.")

37. See *United States v. Caronia*, 703 F.3d 149, 157 (2d Cir. 2012) (outlining two charges brought against the defendant: "[c]ount [o]ne: [c]onspiracy to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a) and 333(a)(2); and [c]ount [t]wo: [i]ntroducing a misbranded drug, Xyrem, into interstate commerce, in violation of 21 U.S.C. §§ 331(a) and 333(a)(2)").

misdeemeanor for off-label promotion of a sinus balloon catheter.³⁸ Although the prosecutor urged the judge to impose a six-month prison sentence, the judge instead fined Facticeau \$1 million.³⁹

Those who support banning manufacturer off-label promotion cite public safety concerns. They argue that physicians should make medical decisions unclouded “by misinformation from a company trying to build its bottom line.”⁴⁰ Further, they contend that this approach prevents unreasonable risk, and preserves the current regulatory scheme by providing manufacturers with an incentive to seek FDA approval for any additional uses of an approved drug.⁴¹ Opponents argue that banning off-label promotion increases the cost of drug and device production and prohibits manufacturers from sharing—and doctors from receiving—important true information.⁴² As for public safety concerns, they maintain that tort liability provides a sufficient deterrent to any misinformation a manufacturer might convey.⁴³

38. United States v. Facticeau, No. 15-CR-10076-ADB, 2020 WL 5517573, at *1–2 (D. Mass. Sept. 14, 2020).

39. Nate Raymond, *Judge Apologizes for Four-Year Delay in Sentencing Former Medical Device Execs at J&J Unit*, REUTERS LEGAL (Jan. 13, 2021, 7:44 PM),

[https://today.westlaw.com/Document/Ie759efe055d811eb999af2e3942ed2d0/View/FullText.html?transitionType=Default&contextData=\(sc.Default\)&firstPage=true..](https://today.westlaw.com/Document/Ie759efe055d811eb999af2e3942ed2d0/View/FullText.html?transitionType=Default&contextData=(sc.Default)&firstPage=true..); see also 21 U.S.C. § 333(a)(2) (2019) (“[I]f any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than \$10,000, or both.”).

40. Greene, *supra* note 21, at 648 (quoting Press Release, U.S. Dep’t of Justice, *Eli Lilly and Company Agrees to Pay \$1.415 Billion To Resolve Allegations of Off-Label Promotion of Zyprexa* (Jan. 15, 2009), available at <http://www.justice.gov/opa/pr/2009/January/09-civ-038.html>).

41. Stephanie M. Greene & Lars Noah, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 243 (2014).

42. 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, 305–06 (2010).

43. *Id.* at 305.

B. THE FIRST AMENDMENT AND COMMERCIAL SPEECH

Although most defendants charged with off-label promotion choose to settle, a few have challenged the FDA's off-label promotion ban, claiming that it violates the First Amendment.⁴⁴ The First Amendment of the United States Constitution protects against state actions that "abridg[e] the freedom of speech."⁴⁵ The First Amendment is an essential, yet sometimes necessarily limited, guarantee.⁴⁶ Commercial speech is one situation in which First Amendment guarantees are limited.⁴⁷ Initially, the Supreme Court construed the First Amendment to lend no protections to commercial speech.⁴⁸ However, the Court eventually extended some First Amendment protection to commercial speech.⁴⁹ Early on, such protection was fairly limited. Through a number of more recent decisions, the Court has afforded additional First Amendment protection, leading some to conclude that there is now little if any distinction between commercial and non-commercial speech.

i. The Birth of the *Central Hudson* Test

The Supreme Court first addressed First Amendment protection of commercial speech in the 1942 case, *Valentine v. Chrestensen*.⁵⁰ In that case, the Court upheld a New York City Sanitary Code that prohibited street distribution of commercial advertising, holding that the First Amendment does not protect

44. *E.g.*, *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012); *see also* *Greene & Noah*, *supra* note 41, at 241 ("Increasingly, however, pharmaceutical manufacturers have raised the First Amendment as a defense to (or even in anticipation of) such charges.").

45. U.S. CONST. amend. I.

46. *E.g.*, Bradford W. Scharlott, *The First Amendment Protection of Advertising in the Mass Media*, in *ADVERTISING AND COMMERCIAL SPEECH* 1, 2 (Theodore R. Kupferman, ed. 1990) (explaining that the government has an interest in regulating commercial speech to ensure the public is not subject to false or misleading advertisements).

47. *E.g.*, *id.*

48. *See infra* Section I.B.i.

49. *See infra* Section I.B.ii.

50. 316 U.S. 52 (1942); *see also* *Wiersum*, *supra* note 18, at 492.

such speech.⁵¹ More than three decades later, however, in *Bigelow v. Virginia*, the Supreme Court retreated from *Valentine*.⁵² The Court held that a Virginia statute banning advertisements for abortion—an attempt to get around the recent decision in *Roe v. Wade*⁵³—violated the First Amendment.⁵⁴ In its decision, the Court described *Valentine* as “distinctly a limited” holding that “obviously does not support any sweeping proposition that advertising is unprotected per se.”⁵⁵

One year later, the Court expanded the First Amendment protection of commercial speech.⁵⁶ In *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, the Court held that, because the speaker has an interest in freedom of commercial speech, and because consumers should be informed, the First Amendment protects commercial speech.⁵⁷ In evaluating the constitutionality of a Virginia statute that prohibited pharmacists from advertising prices, the Court recognized that “[i]t is precisely this kind of choice, between the dangers of suppressing information, and the dangers of its misuse if it is freely available, that the First Amendment makes for us.”⁵⁸ Virginia could not impose professional standards on pharmacists “by keeping

51. *Valentine v. Chrestensen*, 316 U.S. 52, 54–55 (1942) (“Whether, and to what extent, one may promote or pursue a gainful occupation in the streets, to what extent such activity shall be adjudged a derogation of the public right of user, are matters for legislative judgment. The question is not whether the legislative body may interfere with the harmless pursuit of a lawful business, but whether it must permit such pursuit by what it deems an undesirable invasion of, or interference with, the full and free use of the highways by the people in fulfillment of the public use to which streets are dedicated. If the respondent was attempting to use the streets of New York by distributing commercial advertising, the prohibition of the code provision was lawfully invoked against his conduct.”); see also *Wiersum*, *supra* note 18, at 492.

52. *Bigelow v. Virginia*, 421 U.S. 809, 820 (1975) (“[*Valentine*] obviously does not support any sweeping proposition that advertising is unprotected per se.”)

53. 410 U.S. 113 (1973).

54. *Bigelow*, 421 U.S. at 818 (“The fact that the particular advertisement in appellant’s newspaper had commercial aspects or reflected the advertiser’s commercial interests did not negate all First Amendment guarantees.”).

55. *Id.* at 819–20.

56. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976).

57. *Id.* at 760–71.

58. *Id.* at 770.

the public in ignorance of the entirely lawful terms that competing pharmacists are offering.”⁵⁹ The Court emphasized that its holding did not suggest that commercial speech could not be regulated.⁶⁰ In dissent, Justice Rehnquist correctly predicted⁶¹ that the majority’s holding would lead pharmacists to “energetically promote their [drug] sale.”⁶²

The Court adopted intermediate scrutiny for First Amendment protection of commercial speech in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York* when it struck down a New York state restriction on electric company promotional advertisements.⁶³ Under *Central Hudson*, the Court must first determine whether the First Amendment protects the speech.⁶⁴ For commercial speech to be protected by the First Amendment, “it at least must concern lawful activity and not be misleading.”⁶⁵ Next, the Court evaluates whether the “asserted governmental interest is substantial.”⁶⁶ Then, the Court determines if the regulation directly advances that governmental interest.⁶⁷ Finally, the Court asks whether the regulation is “no more extensive than is necessary to serve that interest.”⁶⁸ Thus, under *Central Hudson*, a regulation of commercial speech survives First Amendment review if it directly advances a substantial governmental interest through means no more extensive than is necessary.⁶⁹ And significantly, under *Central Hudson*, the First Amendment does not protect false or misleading commercial speech.⁷⁰

59. *Id.*

60. *Id.* at 770–71 (“In concluding that commercial speech, like other varieties, is protected, we of course do not hold that it can never be regulated in any way. Some forms of commercial speech regulation are surely permissible. We mention a few only to make clear that they are not before us and therefore are not foreclosed by this case.”).

61. Wiersum, *supra* note 18, at 495.

62. *Va. State Bd. of Pharmacy*, 425 U.S. at 788 (Rehnquist, J., dissenting).

63. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557, 557 (1980).

64. *Id.* at 566.

65. *Id.*

66. *Id.*

67. *Id.*

68. *Id.*

69. *Id.*; *see also* Wiersum, *supra* note 18, at 496.

70. *Cent. Hudson Gas & Elec. Corp.*, 447 U.S. at 566.

ii. The Evolution of the *Central Hudson* Test

Although *Central Hudson* has not been overturned, recent cases have broadened First Amendment protection over commercial speech.⁷¹ For example, in *Rubin v. Coors*, the Court claimed to apply *Central Hudson*, yet it imposed new requirements—that the rule advance the government’s interest in a “direct and material way” and that a regulation could not have any less restrictive alternatives.⁷²

In 2020, in *International Outdoor, Inc. v. City of Troy*, the Sixth Circuit created a circuit split by announcing that a content-based speech restriction receives strict scrutiny, even where the restriction concerns commercial speech.⁷³ The court emphasized language from the Supreme Court in *Reed v. Town of Gilbert* explaining that laws that are content-based, either on their face or in their justification, are subject to strict scrutiny, thus “a court must evaluate each question before it concludes that the law is content neutral and thus subject to a lower level of scrutiny.”⁷⁴ According to the Sixth Circuit, *Reed* requires that *Central Hudson* and intermediate scrutiny only apply to content-neutral commercial speech restrictions.⁷⁵ The court criticized a number of post-*Reed* circuit court decisions that applied *Central Hudson* to content-based speech restrictions.⁷⁶

Under *International Outdoor*, a court must first determine if a speech restriction is content-based.⁷⁷ “Regulation of speech is content-based . . . if a law applies to particular speech because of the topic discussed or the idea or message expressed; some obvious facial distinctions based on a message include defining regulated speech by particular subject matter or by its function or purpose.”⁷⁸ If the court determines that the speech restriction

71. Wiersum, *supra* note 18, at 500–11.

72. *Rubin v. Coors*, 514 U.S. 476, 490–91 (1995).

73. *Int’l Outdoor, Inc. v. City of Troy*, 974 F.3d 690, 703 (6th Cir. 2020) (“It follows that the intermediate-scrutiny standard applicable to commercial speech under *Central Hudson*, . . . applies only to a speech regulation that is content-neutral on its face. That is, a regulation of commercial speech that is not content-neutral is still subject to strict scrutiny under *Reed*.”).

74. *Id.* at 703 (quoting *Reed v. Town of Gilbert*, 576 U.S. 155, 166 (2015)).

75. *Id.*

76. *Id.* at 703–06 (noting, in one example, that “instead of applying the *Reed* standard, the court proceeded without much explanation to apply the *Central Hudson* standard”).

77. *Id.* at 703.

78. *Id.* (internal quotations omitted).

is content-based, then under strict scrutiny, the restriction is “presumptively unconstitutional and may be justified only if the government proves that [it is] narrowly tailored to serve compelling state interests[.]”⁷⁹

If reasoning similar to *International Outdoor* is accepted by the Supreme Court, it will constitute a significant expansion of commercial speech protection. Under the early application of *Central Hudson*, in order to survive a First Amendment challenge, a commercial speech restriction was required to directly advance a substantial governmental interest through means no more extensive than is necessary.⁸⁰ In contrast, under the modern application of *Central Hudson*, a speech restriction must also advance the government’s interest in a “direct and material way” and may not have a less restrictive alternative.⁸¹ And under *International Outdoor*, in the Sixth Circuit, content-based commercial speech restrictions must be narrowly tailored and serve a compelling state interest.⁸²

C. COMMERCIAL SPEECH AND OFF-LABEL PROMOTION

Cases applying the First Amendment to commercial speech regarding pharmaceuticals have similarly moved closer to a strict scrutiny approach. In *Sorrell v. IMS Health Inc.*, the Supreme Court invalidated a Vermont law that prohibited pharmacies from selling “records that reveal the prescribing practices of individual doctors” to pharmaceutical companies.⁸³ While permitting others to acquire this data, the Vermont law sought to prevent pharmaceutical manufacturers from obtaining or using it to market brand-name drugs directly to individual doctors.⁸⁴

Sorrell concluded that the law “enacts content- and speaker-based restrictions” on protected speech and thus required “heightened scrutiny” under the First Amendment.⁸⁵ Rejecting the claim that “heightened judicial scrutiny” did not apply to “mere commercial regulation,” the Court nonetheless declined to

79. *Id.* (internal quotations omitted).

80. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n of N.Y.*, 447 U.S. 557, 566 (1980).

81. *Rubin v. Coors*, 514 U.S. 476, 490–91 (1995).

82. *Int’l Outdoor, Inc.*, 974 F.3d at 703.

83. *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 557 (2011).

84. *Id.*

85. *Id.* at 566–67.

decide whether to apply “a special commercial speech inquiry” (i.e., *Central Hudson*) or “a stricter form of judicial scrutiny.”⁸⁶ Instead, it held that the Vermont law failed under either analysis because it was not sufficiently narrowly drawn to advance the State’s asserted interests in, *inter alia*, protecting medical privacy, avoiding harassment of physicians, improving public health, and reducing healthcare costs.⁸⁷

Justice Breyer, joined by Justice Ginsburg and Justice Kagan, dissented. The dissent found that Vermont’s “effort to regulate a commercial enterprise” did not require any “special ‘heightened’ standard of review” beyond the *Central Hudson* test.⁸⁸ Indeed, the dissent argued that the Supreme Court had never applied content-based and speaker-based categorizations to commercial speech.⁸⁹ Further, it warned that whatever First Amendment standard applied to Vermont’s law would likewise apply to “similar regulatory actions,” including those taken by the FDA.⁹⁰ The dissent closed with a significant warning: “[a]t best the Court opens a Pandora’s Box of First Amendment challenges to many ordinary regulatory practices that may only incidentally affect a commercial message. At worst, it reawakens *Lochner*’s pre-New Deal threat of substituting judicial for democratic decisionmaking where ordinary economic regulation is at issue.”⁹¹

True to Justice Breyer’s prediction, in *Caronia*, the Second Circuit applied *Sorrell* to FDA regulations.⁹² *Caronia* is, to date, the most directly on point case involving a First Amendment challenge to a prosecution for off-label promotion. The defendant, Caronia, appealed his conviction for misdemeanor conspiracy to introduce a misbranded drug into interstate commerce under 21 U.S.C. §§ 331(a) and 331(a)(1), arguing that he was convicted for his protected speech.⁹³ The appellate court agreed, holding that “the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for

86. *Id.* at 566–71.

87. *Id.* at 568.

88. *Id.* at 581 (Breyer, J., dissenting).

89. *Id.* at 588 (Breyer, J., dissenting).

90. *Id.* at 586 (Breyer, J., dissenting).

91. *Id.* at 602–03 (Breyer, J., dissenting) (referring to Supreme Court case *Lochner v. New York*, 198 U.S. 45 (1905)).

92. *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012).

93. *Id.* at 152.

speech promoting the lawful, off-label use of an FDA-approved drug” that is not false or misleading.⁹⁴

The court first determined that the government prosecuted Caronia for his speech, and did not merely use his speech as evidence of intent to misbrand.⁹⁵ Next, the court applied *Sorrell* and held that the FDA ban was subject to heightened scrutiny because it is both content-based and speaker-based.⁹⁶ Yet, after determining that it would apply heightened scrutiny, the court then applied *Central Hudson*.⁹⁷ The court first found that the speech concerned a lawful activity, off-label uses, and the speech was not false or misleading.⁹⁸ Although it found the government’s interest “in drug safety and public health” substantial, the court held that the off-label promotion ban does not directly advance that interest.⁹⁹ The ban’s paternalism, the fact that off-label use is legal, and the claim that the speech at issue was not misleading supported the determination that the ban does not directly advance the government’s interest.¹⁰⁰ Similarly, the court found that the “complete and criminal ban on off-label promotion by pharmaceutical manufacturers” is not narrowly drawn.¹⁰¹ The ban, the court concluded, “is more extensive than necessary to achieve the government’s substantial interests.”¹⁰² The court therefore held that the off-label promotion ban failed under heightened *Central Hudson* scrutiny.¹⁰³ Yet, citing the canon of constitutional avoidance, the court did not strike down

94. *Id.* at 164–69.

95. *Id.* at 161.

96. *Id.* at 164.

97. *Id.* at 165–69.

98. *Id.* at 165. Although it likely could have, the FDA did not claim that Caronia’s speech was false or misleading. *Id.* at 165 n.10 (“The government did not argue at trial, nor does it argue on appeal, that the promotion in question was false or misleading.”).

99. *Id.* at 167.

100. *Id.* at 166–67.

101. *Id.* at 167.

102. *Id.*

103. *See id.* at 168.

the ban.¹⁰⁴ Rather it concluded that “the truthful off-label promotion of FDA-approved prescription drugs” is outside the scope of the FDA’s off-label promotion ban.¹⁰⁵

Judge Livingston dissented. She argued that the government did not violate the First Amendment because it only used Caronia’s speech as evidence of his motive or intent to commit a misbranding offense.¹⁰⁶ She cautioned that “the majority calls into question the very foundations of our century-old system of drug regulation.”¹⁰⁷ The FDA chose not to seek certiorari or *en banc* review of the decision in *Caronia*.¹⁰⁸

The Southern District of New York subsequently applied *Caronia* in *Amarin Pharma, Inc. v. United States Food and Drug Administration*, where, in a turn of events, the drug manufacturer sued the FDA.¹⁰⁹ Amarin sought a declaratory judgment permitting it to promote an off-label use of its drug Vascepa through truthful and non-misleading speech.¹¹⁰ Amarin claimed that “the FDA’s threat of a misbranding action [wa]s chilling it from engaging in constitutionally protected truthful speech.”¹¹¹ Responding to Amarin’s request for preliminary relief, the court addressed two important FDA arguments, ruling against the FDA in each.¹¹² First, the court rejected the FDA’s claim that it

104. *Id.* at 160 (“Thus, under the principle of constitutional avoidance, explained *infra*, we construe the FDCA as not criminalizing the simple promotion of a drug’s off-label use because such a construction would raise First Amendment concerns. Because we conclude from the record in this case that the government prosecuted Caronia for mere off-label promotion and the district court instructed the jury that it could convict on that theory, we vacate the judgment of conviction.”).

105. *Id.* at 168–69 (“Our conclusion is limited to FDA-approved drugs for which off-label use is not prohibited, and we do not hold, of course, that the FDA cannot regulate the marketing of prescription drugs. We conclude simply 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.”).

106. *See id.* at 172 (Livingston, J., dissenting).

107. *Id.* at 169 (Livingston, J., dissenting).

108. *See Recent Case*, HARV. L. REV., *supra* note 31, at 798 n.41 (2013) (citing Thomas M. Burton, *FDA Won’t Appeal Free-Speech Marketing Decision*, WALL ST. J. (Jan. 23, 2013, 8:20 PM), <http://online.wsj.com/article/SB10001424127887324539304578260323575925>).

109. *See Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 198 (S.D.N.Y. 2015).

110. *See id.*

111. *Id.*

112. *See id.* at 223–24.

was using Amarin’s speech merely as evidence of its intent to sell Vascepa for an unapproved use, rather than regulating the speech itself.¹¹³

Second, the court rejected the FDA’s argument that *Caronia* was a limited holding that applies only to the facts of that particular case.¹¹⁴ The court was entirely unimpressed with this argument, and even stated at a hearing that the court and the FDA “clearly have a very substantial difference of opinion how to read *Caronia*.”¹¹⁵ Instead, the court quoted *Caronia*’s explicit holding where the Second Circuit “conclude[d] simply 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.”¹¹⁶

For the above reasons, and because it found the speech at issue was not false or misleading, the *Amarin* court granted preliminary relief.¹¹⁷ *Amarin* illustrates two key points. First, at least in the Second Circuit, the First Amendment does indeed preclude the FDA from prohibiting truthful and non-misleading off-label promotion. Second, the FDA has been highly reluctant to adjust its off-label promotion strategy, even though it consistently results in losses.

Finally, in 2020, in *United States v. Facticeau*, a court denied the defendants’ motion for acquittal or a new trial based on their convictions for misdemeanor adulteration and misbranding of a medical device.¹¹⁸ The defendants argued, *inter alia*, that the government violated the First Amendment by relying on “truthful, non-misleading speech” to convict them.¹¹⁹ Although the court declined to overturn the conviction, it did acknowledge that there are valid First Amendment and policy concerns about the current regulatory scheme.¹²⁰

113. *See id.* at 223–25.

114. *See id.* at 225.

115. *Id.* at 224.

116. *Id.* at 226 (quoting *United States v. Caronia*, 703 F.3d 149, 168–69 (2d Cir. 2012)).

117. *Id.* at 237.

118. *United States v. Facticeau*, No. 15-CR-10076-ADB, 2020 WL 5517573, at *1 (D. Mass. Sept. 14, 2020).

119. *Id.* at *12.

120. *Id.* at *1 (“There is also a First Amendment overlay that further complicates the analysis. It seems clear that the statutory and regulatory scheme needs to be rethought. Currently there is no statute that specifically prohibits

D. THE FDA'S SPEECH AS INTENT APPROACH

One approach to avoid First Amendment scrutiny that the FDA has taken, and which the courts in *Caronia* and *Amarin* rejected, is to argue the FDA off-label promotion ban does not prohibit speech.¹²¹ Rather, the FDA only uses speech as evidence of intent to introduce misbranded drugs into the market.¹²² Because, under this theory, the FDA does not ban speech, the misbranding statutes and regulations do not restrict protected expression under the First Amendment. This argument finds support in *Wisconsin v. Mitchell*, where the Supreme Court held that the First Amendment “does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.”¹²³ Advancing this argument in her *Caronia* dissent, Judge Livingston offered the following illustration:

There might be no law forbidding the consumption of arsenic. But this would not endow Abby and Martha with a First Amendment right to offer arsenic laced wine to lonely old bachelors with the intent that they drink it. And any statements Abby or Martha made suggesting their intent—even if all of the statements were truthful and not misleading—would not be barred from evidence by the First Amendment simply because arsenic might legally be consumed.¹²⁴

In sum, the First Amendment protection of commercial speech is expanding. While the FDA maintains that its off-label promotion ban does not violate the First Amendment, many courts that have heard the issue have not agreed.

off-label marketing and yet the Government continues to prosecute the conduct by patching together the misbranding and adulteration regulations, thereby criminalizing conduct that it is not entirely clear Congress intended to criminalize.”).

121. See, e.g., *United States v. Caronia*, 703 F.3d 149, 172 (2d Cir. 2012) (Livingston, J., dissenting).

122. *Id.* at 161 (“Even assuming the government can offer evidence of a defendant’s off-label promotion to prove a drug’s intended use and, thus, mislabeling for that intended use, that is not what happened in this case.”).

123. *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993); see also *Greene*, *supra* note 21, at 679.

124. *Caronia*, 703 F.3d at 175 (Livingston, J., dissenting).

II. STRIKING THE FDA OFF-LABEL PROMOTION BAN IS UNDESIRABLE

As some commentators have noted,¹²⁵ it seems very likely that the Supreme Court will eventually consider the FDA's power to regulate off-label promotion. Moreover, narrowing or striking down the FDA's off-label promotion ban is entirely in line with recent First Amendment precedent.¹²⁶ However, striking the off-label promotion ban will impede the FDA's ability to effect its important goals of "protecting the public health by ensuring the safety, efficacy, and security of . . . drugs."¹²⁷

Recall that FDA approval means that the benefits of a drug outweigh the harms for a certain use. Because approval considers only factors for that particular use, it may be significantly easier for a drug to gain FDA approval where the need is great.¹²⁸ Take Actiq, the drug discussed above that has contributed to the opioid crisis. When the FDA approved Actiq for opioid tolerant cancer patients, it weighed the benefits of providing relief to extreme pain where other milder pain relief was ineffective, against any and all dangers associated with Actiq.¹²⁹ In that narrow situation, the FDA determined that the drug warranted approval.¹³⁰ But had Cephalon submitted Actiq to the FDA for migraines, approval might well have been denied. Thus—absent

125. Wiersum, *supra* note 18, at 288 ("Sooner or later, FDA will have to contend with the protections that commercial speech has gained over the past four decades.").

126. See *Recent Case*, HARV. L. REV., *supra* note 31, at 800 ("Although Caronia is defensible as a matter of constitutional doctrine, it is undesirable as a matter of policy.").

127. U.S. Food & Drug Admin., *supra* note 10.

128. Katherine A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 164 (2007) ("From a pharmaceutical industry perspective, however, once a drug is approved for a first use, off-label sales expand, sometimes by many multiples. This market fact encourages manufacturers to seek FDA approval only for the narrowest, most easy to support indications and then reap the benefits of off-label sales.").

129. Cf. FDA's Actiq Label, *supra* note 5 ("[Actiq] is an opioid analgesic indicated only for management of breakthrough cancer pain in patients 16 and older with malignancies who are *already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain*" (emphasis in original)).

130. Cf. *id.*

an off-label promotion ban—a manufacturer has a strong incentive to seek approval only for a narrow use, especially where the need is grave.¹³¹ Then, once the drug is approved for that use, the manufacturer could simply promote the drug for other uses. That promotion would likely even be truthful in a sense. Actiq, for example, does mitigate migraine pain.¹³² However, the off-label use would lack examination and approval by an unbiased third party to determine that the particular use is both safe and effective.

The opioid epidemic demonstrates that there must be some government regulation to determine which uses that might be marketed are safe. And it stands as a strong reminder that permitting off-label promotion tends to delay, or perhaps prevent altogether, FDA review of new uses for already approved drugs. When a company stands to make a significant amount of money by promoting a drug—perhaps even an addictive drug—in inappropriate circumstances, some companies will exploit that opportunity. And some will do so despite the potential for significant harm to the public.

In extreme cases, to argue that such examination and approval is unnecessary calls into question the entire FDA premarket approval process.¹³³ If manufacturers are permitted to present any studies or promotion materials to doctors under the assumption that doctors are educated and can determine on their own if the evidence is sufficient to determine that a drug is reasonably safe,¹³⁴ then what purpose does the FDA premarket approval process serve?¹³⁵

131. See, e.g., Greene & Noah, *supra* note 41, at 243.

132. See Stephen H. Landy, *Oral Transmucosal Fentanyl Citrate for the Treatment of Migraine Headache Pain in Outpatients: A Case Series*, 44 *HEADACHE* 762, 764 (2004).

133. Greene & Noah, *supra* note 41, at 245.

134. See Greene, *supra* note 21, at 692 (explaining that “courts have viewed doctors, the targets of detailing, as sophisticated customers” in the context of off-label promotion).

135. See *United States v. Caronia*, 703 F.3d 149, 178–79 (2d Cir. 2012) (Livingston, J., dissenting) (“The FDCA’s prohibition on off-label marketing directly advances this interest. If drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses. Prohibiting such promotion is thus ‘one of the few mechanisms available’ to encourage participation in the approval process. And premarket approval improves drug safety and effectiveness only to the extent that drugs are not sold without such approval . . . Furthermore, allowing drug manufacturers to promote off-label uses would undermine the FDA’s approval

As the discussion above illustrates, the off-label promotion ban is essential to allow the FDA to protect the public. In the case of off-label promotion of opioids, where prescription opioids were involved in 32% of 47,000 opioid overdose related deaths in 2018,¹³⁶ it is key to the FDA's mission. The opioid epidemic is not a unique event, instead, it is merely illustrative of the need for an off-label promotion ban. For example, manufacturers have noticed the COVID-19 pandemic is an opportunity to market off-label. The FDA has sent a number of warning letters to manufacturers who claim their drugs can treat COVID-19.¹³⁷ Off-label prescribing may be desirable where, as is currently the case with COVID-19, on-label treatments are lacking. However, the FDA must be able to regulate off-label promotion. Otherwise, some profit-seeking manufacturers may take advantage of the public desperation for new treatments by promoting drugs for unapproved uses, claiming that they provide treatment that is in fact not effective, or ignoring dangerous side effects. If the FDA is to carry out its mission of protecting public health, it must be able to regulate such conduct.

III. A REGULATORY AND LITIGATION STRATEGY

As the discussion above demonstrates, First Amendment review of commercial speech restrictions is getting more demanding, regardless of whether it is called "intermediate," "heightened," or "strict" scrutiny. Unfortunately, the FDA has so far failed to adapt. As one commentator noted, the FDA's "response

process for not only new uses of pre-approved drugs, but also for entirely new drugs. As explained above, when determining whether a drug should be approved, the FDCA requires consideration not only of the drug's safety, but also its effectiveness . . . If a drug manufacturer must be allowed to distribute a drug for any use so long as it is approved for one use, the government's balancing of a drug's benefits against its risks becomes very difficult or even impossible. Drugs viewed as safe for certain uses might be considered unsafe overall if the benefits and risks being weighed are not for a specific intended use but rather for any use at all, whether supported by evidence or not." (internal citations omitted).

136. Ctr. for Disease Control & Prevention, *The Drug Overdose Epidemic: Behind the Numbers*, CDC.GOV (Mar. 25, 2021), <https://www.cdc.gov/drugoverdose/data/index.html>.

137. U.S. Food & Drug Admin., *Fraudulent Coronavirus Disease 2019 (COVID-19) Products*, FDA.GOV (Jan. 29, 2021), <https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products>.

to these series of losses was not to reevaluate its approach . . . strategically choos[e] not to appeal losses, and generally attempt[] to carry on business as usual.”¹³⁸ The FDA’s drug approval framework does not contemplate the current First Amendment problems, because it pre-dates any First Amendment protection of commercial speech.¹³⁹ To protect its regulation of off-label promotion, the FDA should pass regulations that only prohibit false and misleading off-label promotion. The FDA can also preserve regulation of off-label promotion through a new litigation strategy, where it emphasizes evidence showing that the off-label promotion was false or misleading.

A. REGULATIONS THAT SURVIVE FIRST AMENDMENT CHALLENGES

The FDA should pass regulations that explicitly prohibit false and misleading off-label promotion, while acknowledging that some forms of true speech are constitutionally protected. Explicitly in those regulations, the FDA should continue to criminalize false off-label promotion. However, it should switch its approach to misleading speech, instead pursuing only civil remedies. In its new regulations, the FDA should clearly define “false and misleading.”

i. Criminal False Speech and Civil Misleading Speech

Regardless of whether the FDA alleges it, most FDA off-label promotion prosecution involves false or misleading speech.¹⁴⁰ By explicitly prohibiting only false and misleading speech, the FDA will put itself in a strong position to survive First Amendment scrutiny without sacrificing its power to pursue most of the cases that it would under its current structure. Because criminal prosecution is a strong deterrent, and because false speech is easier to identify, the FDA should continue to criminally prosecute false off-label promotion. False promotion has the greatest potential for harm and should thus have the most severe consequences.

138. Wiersum, *supra* note 18, at 488.

139. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 226–27 (S.D.N.Y. 2015).

140. *Recent Case*, HARV. L. REV., *supra* note 31, at 802 n.41 (2013) (citing Thomas M. Burton, *FDA Won’t Appeal Free-Speech Marketing Decision*, Wall St. J. (Jan. 23, 2013, 8:20 PM), <http://online.wsj.com/article/SB10001424127887324539304578260323575925>).

However, the FDA should adjust its approach to misleading speech by pursuing only civil remedies. Prohibiting misleading off-label promotion under a civil scheme would have a number of benefits. First, under a civil approach the FDA would not have to prove beyond a reasonable doubt that the information was misleading. This would allow the FDA to pursue cases where the off-label promotion was misleading as long as a preponderance of the evidence shows that it was misleading. Moreover, changing off-label promotion sanctions from criminal to civil would alleviate some concerns regarding notice.¹⁴¹ Whether information is misleading is likely a fact intensive question. Criminalizing the spread of misleading information thus does not necessarily put the public on notice of what is considered criminal conduct. However, a more fact-based subjective approach is more appropriate in a civil action. A civil statute or regulation prohibiting misleading off-label promotion could thus allow the FDA to pursue its goals without encountering challenges that a similar criminal statute would face. These benefits, in turn, would support the FDA's claim, under a possible First Amendment challenge, that its approach advances its interest in a "direct and material way" that does not have any less restrictive alternatives.¹⁴² Thus, even if a court is not persuaded that the FDA is only regulating false or misleading speech, the FDA is still likely to succeed.

ii. Defining False and Misleading Speech

To avoid First Amendment scrutiny, the FDA must define "false and misleading" either in line with, or narrower than First Amendment doctrine does. Because false is more straightforward to define, this Note focuses on how the FDA can define misleading. Under the commercial speech doctrine, "when the particular content or method of the advertising suggests that it is *inherently* misleading or when experience has proved that in fact

141. See, e.g., *Amarin Pharma, Inc.*, 119 F. Supp. 3d at 215 ("Amarin moved primarily under the First Amendment, but alternatively, under the due process clause, on the ground that the FDA's regulations as to misbranding were vague and did not 'fairly notify Amarin of what off-label promotion is permitted and what is forbidden.'" (quoting Memorandum of Law in Opposition to Plaintiffs' Motion for Preliminary Injunction, *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 215 (S.D.N.Y. 2015) (No. 15 Civ. 3588) 2015 WL 4387279)).

142. *Rubin v. Coors*, 514 U.S. 476, 490–91 (1995).

such advertising is subject to abuse, the [government] may impose appropriate restrictions.”¹⁴³ However, the government “may not place an absolute prohibition on certain types of *potentially* misleading information . . . if the information also may be presented in a way that is not deceptive.”¹⁴⁴ The Court thus distinguishes between inherently misleading speech, which may be entirely banned, and potentially misleading speech, which cannot be absolutely prohibited. Significantly, the “method of advertising” can suggest that speech is inherently misleading. The burden of proof to show that something is misleading is on the government and it “cannot rely on ‘rote invocation’ of misleadingness to meet that burden.”¹⁴⁵

When an agency determines that speech is misleading through “scientific or technical data within its area of expertise,” some courts have adopted a deferential approach to ‘reasoned’ scientific determinations — in practice, leaning on agency assessment for the misleadingness prong.”¹⁴⁶ This deference makes sense in the context of off-label promotion, where the FDA has expertise on drug safety and efficacy. Under this approach, even with the Court’s somewhat vague definition of misleading, the FDA’s definition should survive First Amendment scrutiny. Even without such deference, a deliberate definition that is not overbroad should survive. Ultimately, the FDA should use its expertise in drug efficacy and safety to explicitly define, in regulation, what constitutes misleading off-label promotion.

One approach that the FDA might try is to define “detailing” as being inherently misleading.¹⁴⁷ Professor Stephanie Greene argues that the FDA can prohibit all off-label promotion done through detailing, because detailing is inherently misleading.¹⁴⁸ In short, her argument is that detailing is vulnerable to undue

143. In re R. M. J., 455 U.S. 191, 203 (1982) (emphasis added).

144. *Id.* (emphasis added).

145. *Recent Case*, HARV. L. REV., *supra* note 31, at 2026 n.52 (2016) (citing *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 658–59 (1985); *Ibanez v. Fla. Dep’t of Bus. & Prof’l Regulation*, 512 U.S. 136, 146 (1994)).

146. *Id.* at 2027 (quoting *Alliance II*, 786 F. Supp. 2d 1, 12 (D.D.C. 2011)).

147. Greene, *supra* note 21, at 690 (“A common sense approach to the issue of off-label detailing is arguing the practice is inherently misleading.”).

148. *Id.* at 690–93.

influence and fraud, that doctors are often persuaded by detailing in ways that the public does not expect, and that claims made during detailing are not verifiable.¹⁴⁹

If the FDA successfully illustrates that detailing is misleading, it has met its burden. It might permissibly, under First Amendment doctrine, shift the burden to a defendant to prove that its detailing was not misleading. The primary benefit of this approach is that detailing happens behind closed doors. In *Caronia*, the FDA had the benefit of an informant and a recording of Caronia's detailing,¹⁵⁰ however that is often not available. Without that evidence, the FDA is blind to what really occurred. It is therefore reasonable to shift the burden to the detailer, who will have unique access to evidence related to the promotion in question.

B. LITIGATION STRATEGIES TO SURVIVE FIRST AMENDMENT CHALLENGES

The FDA has tried to defeat First Amendment challenges at the outset by arguing that it is not limiting or restricting speech at all. Rather, the FDA argues it is using speech as evidence of intent to misbrand.¹⁵¹ This argument is appealing because it would allow the off-label promotion ban to stand as it is. However, the FDA should move on from this approach. The FDA has not found much success with this argument.¹⁵² Notably the majority in *Caronia* rejected the intent argument because, in its view, the theory of the government's prosecution was in fact aimed at Caronia's speech advocating off label uses and not at

149. *Id.* at 609–95.

150. *United States v. Caronia*, 703 F.3d 149, 156–57 (2d Cir. 2012).

151. *Id.*

152. *E.g.*, *United States v. Vascular Solutions, Inc.*, No. 5:14-CR-00926 (W.D. TX. Feb. 26, 2016); *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) (“The question is whether this use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid. In fact, the First Amendment allows ‘the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.’ Thus it is constitutionally permissible for the FDA to use speech, in the form of labeling” (internal citations omitted)); *see also* Wiersum, *supra* note 18, at 554 (“Nevertheless, FDA has scored several recent partial victories using its speech as intent theory. In February 2016, a jury acquitted the CEO of Vascular Solutions (“VSI”) in a trial regarding marketing of a medical device for an unapproved use—a closely related issue to marketing of a drug for an off-label use.”).

any intent to misbrand the drug.¹⁵³ The *Amarin* court rejected the argument because the FDA's evidence of intent argument failed to meet the act requirement of misbranding.¹⁵⁴ Because there are strong counter arguments to this approach, and because the FDA has not had much success with it, the FDA is better off focusing its arguments at litigation on other strategies.

If the FDA prohibits only false and misleading off-label promotions, it should be able to avoid First Amendment scrutiny. Under one prong of *Central Hudson* that has yet to be narrowed or overruled, the First Amendment does not protect false or misleading commercial speech.¹⁵⁵ As a litigation strategy, the FDA should emphasize evidence of false or misleading statements in all cases, rather than asserting it can ban all speech. For example, in *Caronia*, the FDA could have easily shown that Caronia's speech was false or misleading.¹⁵⁶ Caronia claimed that the drug he promoted off-label was "a very safe drug" despite his

153. *Caronia*, 703 F.3d at 161–62 ("First, the government's contention that it did not prosecute Caronia for promoting the off-label use of an FDA-approved drug is belied by its conduct and arguments at trial . . . Second, the government's assertion now that it used Caronia's efforts to promote Xyrem for off-label use only as evidence of intent is simply not true . . . Third, the government's summation and the district court's instruction left the jury to understand that Caronia's speech was itself the proscribed conduct . . . Fourth, the government clearly prosecuted Caronia for his words—for his speech. A pharmaceutical representative's promotion of an FDA-approved drug's off-label use is speech.").

154. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 223 (S.D.N.Y. 2015).

155. *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557, 566 (1980).

156. *Greene & Noah*, *supra* note 41, at 244 ("Had the truthfulness or misleading nature of Caronia's claims been at the heart of the case, the court's analysis would have been quite different. The Supreme Court has held that the government is 'free to prevent the dissemination of commercial speech that is false, deceptive, or misleading, or that proposes an illegal transaction.'" (citing *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 638 (1985))).

knowledge of the drug's dangerous side effects—including depression and death.¹⁵⁷ However, the FDA did not allege that the speech was false,¹⁵⁸ a decision that likely led to the Agency's loss.

Another litigation strategy responds to a frequent argument against the FDA's off-label promotion ban that relies on the Supreme Court's recurring observations that commercial speech restrictions cannot be justified by paternalism.¹⁵⁹ Justice Blackmun summarized this line of arguments in *Virginia State Board of Pharmacy*, asserting that “information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.”¹⁶⁰

In its future litigation, the FDA should emphasize two important reasons why the paternalism argument is inapplicable in this context: (1) research suggests that the “learned intermediaries” argument is false, and (2) the party harmed is not the party hearing the speech. First, some courts argue that doctors are “learned intermediaries” who “safeguard their patients from the aggressive marketing strategies of pharmaceutical companies.”¹⁶¹ However, detailing does affect doctors' prescribing practices.¹⁶² According to one former pharmaceutical sales representative, “it's the doctors' job to treat patients and not to justify their actions, it's my job to constantly sway the doctors. It's a job I'm paid and trained to do . . . [m]ost of the time [doctors] don't

157. *United States v. Caronia*, 703 F.3d 149, 172 n.3 (2d Cir. 2012) (“Caronia later admitted that his employer required him to meet an annual sales quota of 520 bottles of Xyrem in 2005, the year these conversations took place, and that he was unable to meet it. In fact, the salaries of Orphan's sales personnel depended to a significant degree on meeting sales targets, and in 2005 Caronia was ranked near the very bottom of Orphan's national sales force.”).

158. *Greene & Noah*, *supra* note 41, at 244 (“The truthfulness of [Caronia's] speech, however, was never an issue at trial since the government believed it needed to show only that he promoted the drug for an off-label use.”).

159. *See, e.g.*, Ralph F. Hall & Elizabeth S. Sobotka, *Inconsistent Government Policies: Why FDA Off-Label Regulation Cannot Survive First Amendment Review Under Greater New Orleans*, 62 *FOOD & DRUG L.J.* 1, 47 (2007).

160. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976).

161. *Greene*, *supra* note 21, at 650–51.

162. Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, 4 *PLOS MED.* 621, 623–24 (2007).

even realize that's what they're doing."¹⁶³ Doctors therefore are probably not the "learned intermediaries" that some courts assume they are. And when the risk for harm is so high, paternalism seems appropriate.¹⁶⁴

Second, off-label promotion is unlike other marketing considered under the commercial speech doctrine because "unlike the door-to-door vendors of cosmetics and vacuum cleaners, drug reps do not sell their product directly to buyers. Consumers pay for prescription drugs, but physicians control access."¹⁶⁵ Most patients must trust their doctors when they prescribe a medication, because many patients do not have the information or expertise to question their doctors' prescribing practices.¹⁶⁶ The patients suffer the harm if they take unsafe or ineffective medication, yet it is the doctors whom the paternalism argument seeks to protect. In that sense, patients do not receive information that they can weigh to "perceive their own best interests," as is the case in the typical commercial speech scenario. When patients are so dependent on their doctors, and when doctors rather than patients make prescribing decisions, some paternalism is a necessary protection.

The Actiq story demonstrates the importance of this argument. Patients who were in pain trusted their doctors' prescriptions. Yet, many who took Actiq for off-label uses became addicted, and many died. Should these patients have "perceived their own best interest" before taking the medication that their doctors recommended? Expecting that sort of research and expertise for each drug a patient takes is unreasonable.

163. *Id.* at 624; see also Hannah Fresques, *Doctors Prescribe More of a Drug if They Receive Money from a Pharma Company Tied to It*, PROPUBLICA (Dec. 20, 2019, 12:00 PM), <https://www.propublica.org/article/doctors-prescribe-more-of-a-drug-if-they-receive-money-from-a-pharma-company-tied-to-it>.

164. Cf. Greene & Noah, *supra* note 41, at 241 (2014) ("The practice of detailing raises ethical issues as it may persuade doctors to prescribe unnecessary or more expensive drugs; these concerns are compounded when sales representatives promote off-label uses that have not been proven safe and effective."). *But see* Hall & Sobotka, *supra* note 159, at 16 ("The courts have explicitly rejected paternalism as a valid reason to restrict off-label speech.").

165. Fugh-Berman & Ahari, *supra* note 162, at 621.

166. Tracy Weber & Charles Ornstein, *Why You Should Care About the Drugs Your Doctors Prescribes*, PROPUBLICA (July 15, 2013, 8:57 PM), <https://www.propublica.org/article/why-you-should-care-about-the-drugs-your-doctor-prescribes> ("For most of us, evaluating a doctor's prescribing habits is just about impossible. Even doctors themselves have little way of knowing whether their drug choices fall in line with those of their peers.").

IV. CONCLUSION

The FDA's off-label promotion ban predates First Amendment protection of commercial speech. Yet today, the First Amendment extends substantial protection to commercial speech. Because the off-label promotion ban is essential to the FDA's goal of "protecting the public health by ensuring the safety, efficacy, and security of . . . drugs,"¹⁶⁷ the FDA must adjust its regulatory scheme and litigation strategy to be consistent with the First Amendment. Without the FDA as a neutral party weighing the costs and benefits of a drug's use, prescribers will be exposed to an influx of potentially dangerous off-label promotion. Some manufacturers will end-run the FDA approval process, then promote drugs for unapproved uses. The danger of this practice outweighs its benefits.

167. U.S. Food & Drug Admin., *supra* note 10.
