

IN DEFENSE OF THE FDA'S PROHIBITION AGAINST OFF-LABEL PHARMACEUTICAL MARKETING: THE FIRST AMENDMENT DOES NOT STAND IN THE WAY

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ABSTRACT

In United States v. Caronia, the Second Circuit recently concluded that the Food and Drug Administration's prohibition against off-label pharmaceutical marketing violates the First Amendment's limited protection for commercial speech, contrary to long-standing FDA policy. In Amarin Pharma, Inc. v. United States Food & Drug Administration, the United States District Court for the Southern District of New York followed the Caronia court's holding. It granted a preliminary injunction to a pharmaceutical manufacturer, preventing the FDA from enforcing its prohibition and allowing the manufacturer to market drugs off-label using truthful and non-misleading speech. These judicial decisions represent a significant departure from previous norms in the pharmaceutical industry, where the FDA strictly prohibited and patrolled off-label marketing.

The decisions in Caronia and Amarin arose out of an incorrect application of the Supreme Court's Central Hudson analysis for determining whether a government regulation violates First Amendment protection for commercial speech. The two courts failed to give the government the amount of deference owed to commercial speech regulation, even though the government has a substantial

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interest in ensuring that drugs are safe and effective for human use. The courts should have found that the FDA's prohibition does not violate the First Amendment.

Regardless of the constitutionality of the FDA's prohibition, the policy creates a practical problem. The prohibition prevents useful, beneficial information from circulating freely between pharmaceutical manufacturers and physicians, even while it prevents misleading information from causing harm. Because pharmaceutical sales representatives are not permitted to market off-label, physicians have less access to information about new off-label uses that may be lifesaving to patients. To solve this problem, the FDA should amend its policy to allow pharmaceutical companies to disseminate factual, unbiased information obtained from clinical trials to physicians once the company has submitted a supplemental new drug application to the FDA for approval of a particular off-label use.

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INTRODUCTION

In 2012, the Second Circuit held in *United States v. Caronia*¹ that the United States violated the First Amendment when it construed the misbranding provision of the Federal Food, Drug, and Cosmetic Act (FDCA)² to prohibit off-label³ marketing by pharmaceutical sales representatives and prosecuted a sales

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

2. *See generally* 21 U.S.C. §§ 301-399 (2012). The misbranding provision of the FDCA states, “The following acts and the causing thereof are prohibited: (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.” *Id.* § 331(a) (2015).

3. According to the FDA, “off-label” refers to using a drug in a way that is different from that described in the FDA-approved drug label. *Understanding Unapproved Use of Approved Drugs “Off Label”*, FDA, <http://www.fda.gov/forpatients/other/offlabel/default.htm> [<https://perma.cc/54W5-87P6>] (last updated June 2, 2016). The drug label of FDA-approved drugs gives information about the drug, including the approved doses and how it is to be given to treat the medical condition for which it was approved. *Id.* Moreover, when a drug is used off-label, this can mean that the drug is “[u]sed for a disease or medical condition that it is not approved to treat”; “[g]iven in a different way” (such as by a different route); or “[g]iven in a different dose.” *Id.*

representative based on that construction.⁴ This holding conflicts with established Food and Drug Administration (FDA) regulations and policy.⁵ On August 7, 2015, in *Amarin Pharma, Inc. v. United States Food & Drug Administration*, the United States District Court for the Southern District of New York applied *Caronia* to a pharmaceutical manufacturer's action against the FDA.⁶ In that case, Amarin Pharma, Inc. alleged that the FDA would violate Amarin's First Amendment rights if the FDA enforced misbranding regulations against it as threatened for making truthful and non-misleading statements about an unapproved use of one of Amarin's FDA-approved drugs.⁷ The court clarified the Second Circuit's *Caronia* holding, explaining that not only could the FDA not prosecute pharmaceutical manufacturers and their representatives directly for truthful and non-misleading speech about off-label uses, but that the FDA also could not use truthful and non-misleading speech by manufacturers as evidence of intent to promote the sale of misbranded drugs in interstate commerce.⁸ The court granted Amarin a preliminary injunction to prevent the FDA from prosecuting, based on the likelihood of Amarin's success on the merits of its First Amendment claim.⁹

Through *Caronia*, the Second Circuit implicitly endorsed a novel route for pharmaceutical companies to assert and defend their alleged right to truthfully market drugs for off-label uses by holding that the misbranding provision could not be used to prevent marketing protected by the First Amendment.¹⁰ It thereby frustrated the FDA's policy against dissemination of promotional speech about unapproved uses of drugs and "call[ed] into question the very

4. *Caronia*, 703 F.3d at 169 ("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.").

5. See generally 21 C.F.R. § 99 (1998) and its subparts, which regulate "Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices."

6. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 223-25 (S.D.N.Y. 2015).

7. *Id.* at 198, 219.

8. *Id.* at 227-28.

9. *Id.* at 237.

10. See *id.* at 208 ("The Second Circuit's 2012 decision in *Caronia* addressed, for the first time, the interplay between the FDCA's misbranding provisions and the First Amendment.").

foundations of our century-old system of drug regulation.”¹¹ According to the FDA, the prohibition against off-label marketing ensures that pharmaceutical manufacturers will follow the existing regulatory scheme to obtain approval for subsequent drug uses after initial approval.¹² The regulatory drug approval process is intended to protect the public from unsafe and ineffective drugs.¹³

The Supreme Court has not addressed whether the FDA’s ban on off-label promotion violates the First Amendment,¹⁴ but others have criticized the ban as an unconstitutional prohibition on commercial speech.¹⁵ The *Caronia* and *Amarin* courts agreed with that criticism, and the *Amarin* court noted additionally that the commercial-speech doctrine and First Amendment jurisprudence have outmoded the FDA regulatory scheme of the 1960s.¹⁶ In 1980, the Supreme Court created a four-factor test in *Central Hudson Gas v. Public Service Commission of New York* to determine whether any particular government action violates First Amendment protection of commercial speech.¹⁷ Applying this test, the *Caronia* court held that the FDA’s ban on off-label marketing violated the First Amendment because the ban also prohibited truthful and non-misleading speech.¹⁸

11. *United States v. Caronia*, 703 F.3d 149, 169 (2d Cir. 2012) (Livingston, J., dissenting).

12. *Amarin*, 119 F. Supp. 3d at 226 (“[T]he FDA argues that . . . protecting truthful speech aimed at promoting off-label drug use is ‘a frontal assault . . . on the framework for new drug approval that Congress created in 1962,’ . . . because allowing a manufacturer to promote such use ‘has [] the potential to eviscerate [the] FDA drug approval regime.’” (quoting Memorandum of Law in Opposition to Plaintiffs’ Motion for Preliminary Injunction, *Amarin*, 119 F. Supp. 3d 196 (No. 15 Civ. 3588), 2015 WL 4387279, at *1)).

13. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (“An Act [t]o protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs, authorize standardization of drug names, and clarify and strengthen existing inspection authority . . .”).

14. Brief for Defendant-Appellant, *Caronia*, 703 F.3d 149 (Nos. 09-5006-cr (L), 10-750-cr (CON)), 2010 WL 6351495, at *34-35 (“The issue of non-fraudulent commercial free speech within the drug and device industry has narrowly avoided judicial review until now.”).

15. See, e.g., 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 (2011).

16. See *Caronia*, 703 F.3d at 152; see also *Amarin*, 119 F. Supp. 3d at 226-27.

17. See *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557 (1980). For an in-depth analysis of the *Central Hudson* test, see *infra* Section II.B.

18. See *Caronia*, 703 F.3d at 164-69.

The *Caronia* court misapplied *Central Hudson*, however, and the ban on off-label promotion is necessary to prevent false and misleading information about off-label uses from becoming pervasive and seriously injuring the public.¹⁹ The ban on off-label promotion is constitutional under the *Central Hudson* test because (1) the *Caronia* court examined whether off-label promotion was inherently false and misleading rather than examining whether off-label promotion was more than likely to be false and misleading;²⁰ (2) the speech likely relates to unlawful activity because under the FDCA, pharmaceutical manufacturers may not introduce or cause to be introduced into interstate commerce any drug that is misbranded, i.e., lacking adequate instructions for its intended use;²¹ and (3) the ban is necessary and narrowly tailored to promote the government's substantial interest in protecting public health and safety as well as the integrity of the FDA drug approval process.²²

If the FDA's prohibition on off-label promotion of drugs is constitutional, then a conflict remains between the FDA's goal—ensuring that pharmaceuticals are safe and effective²³—and pharmaceutical manufacturers' objectives—to promote and sell drugs.²⁴ Many scholars have criticized the slow, expensive FDA drug approval process as being outpaced by rapid advancements taking place in pharmaceutical development and by physicians' and patients' needs for new, experimental drugs.²⁵ The solution to this

19. See Kate Greenwood, *The Ban on "Off-Label" Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False or Misleading Commercial Speech?*, 37 AM. J.L. & MED. 278 (2011), for an analysis of the constitutionality of the FDA's off-label promotion ban.

20. See *infra* Subsection IV.A.1.

21. See 21 U.S.C. § 331(a) (2015); *id.* § 352(f) (2013).

22. See *infra* Subsections IV.A.3-4.

23. See 21 U.S.C. § 393(b) (2011); see also Stephanie M. Greene, *Opening Statement: FDA Prohibitions on Off-Label Marketing Do Not Violate Drug Manufacturers' First Amendment Rights*, 162 U. PA. L. REV. ONLINE 239, 246 (2014), <https://www.pennlawreview.com/online/162-U-Pa-L-Rev-Online-239.pdf> [<https://perma.cc/RNQ3-WLRR>].

24. *Id.* at 241 (describing "the practice of sales representatives visiting doctors in their offices to promote drugs," and the likelihood that those representatives will be motivated by sales and profits).

25. See, e.g., Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 178 (1985) ("The bureaucracy at the FDA acquired a reputation for remarkable inefficiency and delay . . . [and] the time and expense of new drug development increased dramatically."); see also 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 (2010) ("Indeed, some have said that off-label prescribing should be encouraged to advance

problem is rooted in physicians' need for reliable scientific information about off-label uses²⁶ that comes from rigorous clinical testing.²⁷ In the current regulatory scheme, the FDA recommends that pharmaceutical sales representatives only distribute "scientific and medical publications on unapproved uses," meaning articles from peer-reviewed scientific and medical journals or reference texts,²⁸

public health in the face of a moribund agency approval process that is underfunded, overwhelmed, and incapable of timely reviewing and approving new indications at a pace consistent with medical developments."); Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 100 (1999) ("[T]he path of a new drug from the moment of conceptualization to its ultimate marketing has been laborious and time-consuming. Many critics suggest that the existing drug approval system entails an excessive number of trials and observations per trial, delaying both the development of new drugs and the optimization of effective dosing.").

26. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 213 (S.D.N.Y. 2015).

27. Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476 (2009). Dresser and Frader explained physicians' need for conclusive clinical trials for off-label indications as follows:

Off-label prescribing can also harm patients, however. The potential for harm is greatest when an off-label use lacks a solid evidentiary basis. A 2006 study examining prescribing practices for 169 commonly prescribed drugs found high rates of off-label use with little or no scientific support. Researchers examining off-label use in U.S. children's hospitals concluded, "[W]e still have incomplete knowledge about the safety and efficacy of many medications commonly used to treat children across a range of drug classes and clinical diagnoses." More than half the respondents in a survey of academic medical centers reported that innovative off-label prescribing raised concerns in their institutions, such as lack of data . . .

...

In a perfect world, all uses of drugs and devices would be supported by solid research.

Id.

28. See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICES 1 (2014), <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm387652.pdf> [<https://perma.cc/E2J8-GDBX>] ("This guidance describes the Food and Drug Administration's . . . current thinking on recommended practices for drug and medical device manufacturers and their representatives to follow when distributing to health care professionals or health care entities scientific or medical journal articles, scientific or medical reference texts, or clinical practice guidelines (CPGs) that discuss unapproved new uses for approved drugs . . . marketed in the United States. For the purpose of this guidance, these materials are generally referred to as *scientific and medical publications*.").

because the FDA will not use dissemination of those texts as evidence of the manufacturer's intent to misbrand drugs.²⁹ In support of its current policy, the FDA explicitly recognizes the importance of communicating truthful, non-misleading information to medical professionals.³⁰ Yet the FDA persists in its position that it cannot guarantee public health and safety without adherence to the full rigors of the new drug approval process.³¹

To accommodate the competing interests in play—including the FDA's interest in drug safety and efficacy, pharmaceutical manufacturers' interest in marketing and selling drugs for new uses, and medical professionals' interest in providing the best health care to patients—the FDA should allow pharmaceutical manufacturers to make certain factual statements about off-label uses of the drugs they develop based on the results of clinical trials.³² A pharmaceutical company should only be given this information-facilitation role, however, after it submits a supplemental new drug application for the off-label use.³³ This would solve the off-label promotion problem in several ways: (1) pharmaceutical representatives would become disseminators of sound research on off-label uses and (2) the FDA would ensure that the information physicians receive is up-to-date, scientifically researched, tested, and proven, if not necessarily conclusive.³⁴

Part I of this Note discusses the legal history of the FDA's regulation of pharmaceutical promotion and focuses on off-label marketing. Part I also analyzes policy arguments from the perspectives of the FDA and pharmaceutical companies. Part II covers the early history of judicial views on commercial speech and

29. *See id.* at 6 (“Consistent with longstanding FDA policy and practice, if manufacturers distribute scientific or medical publications as recommended in this guidance, FDA does not intend to use such distribution as evidence of the manufacturer's intent that the product be used for an unapproved new use.”).

30. *See id.* (“[T]he public health may benefit when health care professionals receive truthful and non-misleading scientific or medical publications on unapproved new uses. This information can be particularly important given that a health care professional can generally choose to use or prescribe an approved or cleared medical product for an unapproved use, if the off-label use is appropriate based on his or her judgment.”).

31. *See id.* (“The narrow ‘safe harbor’ recommended in the guidance was also consistent with FDA's continued belief that FDA premarket review and approval are critical to public health.”).

32. *See infra* Section IV.B.

33. *See infra* Section IV.B.

34. *See infra* Section IV.B.

includes decisions concerning the interaction of commercial speech with the First Amendment. Part III considers two modern court decisions on off-label marketing regulations. Part IV argues that the best solution to the conflict between competing policies is to allow certain restricted commercial speech about off-label uses by pharmaceutical representatives, rather than to entirely prohibit it, in order to ensure that available information about off-label uses is as true and non-misleading as possible, given the advancement of medical knowledge at any time.

I. REGULATORY HISTORY AND POLICY SURROUNDING OFF-LABEL MARKETING

Congress enacted the FDCA in 1938³⁵ in response to the wide availability of unsafe, mislabeled, and adulterated pharmaceuticals for sale in the United States.³⁶ The Pure Food and Drugs Act of 1906,³⁷ the predecessor of the FDCA and creator of the FDA,³⁸ was still in effect when Senator Royal S. Copeland of New York introduced the FDCA as Senate Bill 1944 (S. 1944) in 1933.³⁹ Scholars and the FDA had long criticized the 1906 Act for providing insufficient protection to the public from unsafe drugs.⁴⁰ At the

35. See Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301-399 (2012)).

36. See Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299, 300 (2003).

37. See Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768.

38. See *When and Why Was the FDA Formed?*, FDA, <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm214403.htm> [<https://perma.cc/3M8M-ZSX6>] (last updated Mar. 4, 2016).

39. See S. 1944, 73d Cong. § 26(a) (1933) (“This Act shall take effect six months after the date of approval. The Federal Food and Drugs Act of June 30, 1906, as amended, (U.S.C., title 21, secs. 1-15) shall remain in force until such effective date, and is hereby repealed effective upon such date”); see also David F. Cavers, *The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions*, 6 LAW & CONTEMP. PROBS. 2, 2, 8 (1939).

40. See Cavers, *supra* note 39, at 5-6; see also *Food, Drugs, and Cosmetics: Hearings on S. 1944 Before a Subcomm. of the Comm. on Commerce*, 73d Cong. 58-59 (1933) [hereinafter *Hearing*] (statement of Walter G. Campbell, Chief, Food and Drug Administration). In 1932, scholars Arthur Kallet and F.J. Schlink wrote and published *100,000,000 Guinea Pigs: Dangers in Everyday Foods, Drugs, and Cosmetics*, which criticized the American pharmaceutical and food industries in the United States for selling products to consumers without knowing how those products would affect consumers. See ARTHUR KALLET & F.J. SCHLINK, *100,000,000 GUINEA PIGS: DANGERS IN EVERYDAY FOODS, DRUGS, AND COSMETICS* 251 (1932)

introduction of S. 1944 at a Senate subcommittee hearing, Hon. Henry A. Wallace, the then-Secretary of Agriculture,⁴¹ advocated for the bill and listed improvements it made on the existing legislative scheme, including prohibiting “[f]alse advertising of foods, drugs, and cosmetics,” requiring “[d]efinitely informative labeling,” and providing “[m]ore effective methods for the control of false labeling and advertising of drug products.”⁴² Walter G. Campbell, then-chief of the FDA, spoke at length on new provisions of the bill at the subcommittee hearing, including one provision that required informative labeling to distinguish cures from palliative products.⁴³ As introduced, the bill had two overarching goals: (1) “[t]o prevent the manufacture, shipment, and sale of adulterated or misbranded food, drugs, and cosmetics, and to regulate traffic therein” and (2) “to prevent the false advertisement of food, drugs, and cosmetics.”⁴⁴ The purpose of the bill was to ensure that consumers received accurate information about the drugs they purchased and to protect them from harmful products.⁴⁵

(attributing death, disease, and economic loss to “the indifference and the avarice of the manufacturers of food and drugs”). The book also criticized the existing federal legislation that regulated the industry. See Hazel Kyrk, *Book Reviews: 100,000,000 Guinea Pigs—Dangers in Everyday Foods, Drugs, and Cosmetics*, 6 J. BUS. U. CHI. 352, 352 (1993).

41. Originally, the Department of Agriculture housed the FDA. *FDA’s Origin*, FDA, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm> [<https://perma.cc/G7FE-F7HB>] (last updated June, 23, 2014). It was not until 1980 that the FDA transferred to the Department of Health and Human Services, its current location. *Id.*

42. *Hearing, supra* note 40, at 12 (statement of Hon. Henry A. Wallace, Secretary of Agriculture).

43. *Id.* at 41 (statement of Walter G. Campbell, Chief, Food and Drug Administration) (“[Consumers] should not be sold a remedy labeled as a cure for that disease unless it is a cure for that disease. [Consumers] have the right to buy it intelligently. [Consumers] should have the right to buy it with full knowledge of the fact that it will not operate as a cure if it is merely palliative. This particular paragraph [of the bill] proposes such a requirement.”).

44. S. 1944, *supra* note 39.

45. *Hearing, supra* note 40, at 12 (statement of Hon. Henry A. Wallace, Secretary of Agriculture) (“I think it is generally understood that this bill is intended primarily to protect consumers. At the same time it should operate in the interest of all honest manufacturers.”).

A. Historical Reasons for Enactment of the Food, Drug, and Cosmetic Act

In large part, criticism of the 1906 Act stemmed from tragedies that occurred because consumers ingested and were harmed by unsafe, mislabeled, or adulterated drugs, and existing legislation was ineffective in preventing or punishing manufacturers that sold those drugs.⁴⁶ For example, while speaking in support of S. 1944 and new restrictions on pharmaceutical companies, one scholar warned that taking “dinitrobenzol,” a chemical advertised as a weight-loss remedy, could cause a person’s temperature to rise by nine or ten degrees and that “[w]ithin 24 hours that patient has practically burned himself to death.”⁴⁷ The 1906 Act did nothing to protect against that risk because it did not regulate drug safety.⁴⁸

Despite strong support for the bill from the FDA in 1933, the FDCA was not enacted until five years after its introduction, in 1938.⁴⁹ The drug industry, in particular, forcefully resisted its enactment.⁵⁰ The bill failed to gain the required votes in the 73rd and 74th Congresses, but Senator Copeland introduced a new version each time it was defeated.⁵¹ The “Sulfanilamide Disaster” was the impetus that finally caused Congress to enact the FDCA.⁵² In late

46. See, e.g., *id.* at 11 (“I doubt that anyone will wish to appear before this committee in defense of the many abuses which cannot be remedied under existing legislation; there is too much grim evidence of the tragic effects that almost daily result from the Government’s inability to prevent the shipment and sale of dangerous and worthless products.”); see also *id.* at 46-47 (statement of Yandell Henderson, Professor of Applied Physiology, Yale University) (“I know of cases in which illness, or even death, has occurred from inadequate protection because of the inadequacy of the present law.”).

47. *Id.* at 47 (statement of Yandell Henderson, Professor of Applied Physiology, Yale University). According to the National Center for Biotechnology Information, dinitrobenzenes “are synthetic substances that are used in explosives.” PubChem Open Chemistry Database, *Compound Summary for CID 7452*, NAT’L CTR. BIOTECHNOLOGY INFO., http://pubchem.ncbi.nlm.nih.gov/compound/1_3-Dinitrobenzene#section=Safety-and-Hazards (last visited Nov. 17, 2016). Under the Globally Harmonized System (GHS) for Hazard Communication, the chemical is classified as toxic, hazardous to health, and environmentally damaging. *Id.* § 10.1.1 (under “Hazards Identification: GHS Classification” heading).

48. *Hearing*, *supra* note 40, at 47 (statement of Yandell Henderson, Professor of Applied Physiology, Yale University).

49. Cavers, *supra* note 39, at 2.

50. *Id.* at 8-9.

51. *Id.* at 8-18.

52. Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE (June 1981), <http://www.fda>.

1937, more than one hundred people died after taking Elixir Sulfanilamide, a solution of the antibiotic sulfanilamide dissolved in a toxic solvent called diethylene glycol.⁵³ Although the manufacturer tested Elixir Sulfanilamide to ensure that it met consumer preferences such as fragrance, taste, and appearance, the company did not test for toxicity because existing law did not require toxicity testing.⁵⁴ This tragedy provided the momentum needed for both the House and Senate to pass the FDCA, and President Roosevelt signed it into law on June 25, 1938.⁵⁵

While the Pure Food and Drugs Act of 1906 spanned only five pages in the *United States Statutes at Large*,⁵⁶ the FDCA spanned twenty pages.⁵⁷ Two notable additions formed parts of the bulkier, more comprehensive act: (1) the definition of “new drug”⁵⁸ and (2) the requirement that all new drugs have an approved application on file with the FDA before being introduced into interstate commerce.⁵⁹ Although these provisions were a vast improvement on

gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm [https://perma.cc/JP5H-9KE7]; see also Cavers, *supra* note 39, at 20; Jef Akst, *The Elixir Tragedy, 1937*, SCIENTIST (June 1, 2013), <http://www.the-scientist.com/?articles.view/articleNo/35714/title/The-Elixir-Tragedy--1937/> [https://perma.cc/STX4-6U39]; Dennis B. Worthen, *Pharmaceutical Legislation: An Historical Perspective*, 10 INT’L J. PHARMACEUTICAL COMPOUNDING 20, 24-25 (2006), <http://www.lloydlibrary.org/scholar/Legislation%20final%20pdf.pdf> [https://perma.cc/S944-HVR8].

53. See Ballentine, *supra* note 52; see also Cavers, *supra* note 39, at 20.

54. See Ballentine, *supra* note 52; see also Cavers, *supra* note 39, at 20.

55. See Cavers, *supra* note 39, at 20-22.

56. See Pure Food and Drug Act of 1906, Pub. L. 59-384, 34 Stat. 768.

57. See Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040.

58. *Id.* § 201(p) (“The term ‘new drug’ means—[a]ny drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof”).

59. Worthen, *supra* note 52, at 25; see also Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, § 505(a), (d), 52 Stat. 1040, 1052:

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed . . . is effective with respect to such drug.

...

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such

the 1906 Act, the 1938 FDCA regulated only drug safety but not drug efficacy.⁶⁰ In the 1950s and 1960s, Congress again held hearings on food, drug, and cosmetics issues, which revealed that pharmaceutical companies were marketing their products with false and misleading promotional materials and that consumers and physicians relied on that information to the detriment of public health and well-being.⁶¹ In 1962, both houses of Congress voted unanimously to pass the Kefauver–Harris Amendments to the FDCA,⁶² which added drug efficacy as one of the FDA’s regulatory objectives.⁶³ Today, the FDCA requires pharmaceutical companies to test all new drugs for safety and efficacy before the FDA will approve a new drug application.⁶⁴ If a pharmaceutical manufacturer sells a drug that is not approved by the FDA or not labeled properly, then that sale violates the FDCA.⁶⁵

conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or (4) upon the basis of the information submitted to him as part of the application . . . he has insufficient information to determine whether such drug is safe for use under such conditions, he shall . . . issue an order refusing to permit the application to become effective.

60. See Waxman, *supra* note 36, at 300.

61. *Id.* at 301-02 (“A large part of these hearings focused on the false and misleading promotion of drugs by the pharmaceutical industry. The evidence developed from these hearings demonstrated that a regulatory scheme that depended on postmarket enforcement against false and misleading promotion was grossly inadequate to protect Americans from serious harm. The hearings showed that the pharmaceutical marketplace was filled with misleading promotional material on which physicians relied, that there was no reliable source of evidence from which physicians could tell effective drugs from ineffective drugs, and that many Americans were being subjected unnecessarily to toxic drugs whose benefits had been greatly exaggerated or were nonexistent.”).

62. See *Kefauver-Harris Amendments Revolutionized Drug Development*, FDA CONSUMER HEALTH INFO. 1-2 (Oct. 2012), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm> [<https://perma.cc/XQT8-R66G>].

63. See Drug Amendments of 1962, Pub. L. No. 87-781, § 102(a)(1), 76 Stat. 780, 781 (“Section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act . . . defining the term ‘new drug’, is amended by (A) inserting therein, immediately after the words ‘to evaluate the safety’, the words ‘and effectiveness’, and (B) inserting therein, immediately after the words ‘as safe’, the words ‘and effective.’”).

64. See 21 U.S.C. § 355(d) (2012).

65. See *id.* § 331.

B. Food and Drug Administration's Prohibition Against Off-Label Marketing

The FDCA prohibits drug misbranding through several provisions.⁶⁶ It is the FDA's policy that in combination with the definitions of "misbranded" and "labeling," the misbranding provisions prohibit off-label marketing of pharmaceuticals.⁶⁷ The United States and the FDA cite § 331(a) in particular as the basis for prosecution of pharmaceutical sales representatives who have discussed off-label uses of an FDA-approved drug with prescribing physicians.⁶⁸ Section 331(a) prohibits causing the introduction of a misbranded drug into interstate commerce.⁶⁹ Under the FDCA, a drug is misbranded "[u]nless its labeling bears adequate directions for use" and "adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration . . . as are necessary for the protection of users."⁷⁰ Off-label uses of FDA-approved drugs are considered "new drugs" under the FDCA because off-label uses have not been tested for safety and

66. See *id.* § 331(a)-(c), (g), (k).

67. See GUIDANCE FOR INDUSTRY, *supra* note 28, at 3. The FDA advised, "[T]he modern Federal Food, Drug, and Cosmetic Act . . . and FDA regulations prohibit manufacturers from introducing new drugs . . . into interstate commerce for any intended use that FDA has not determined to be safe and effective." *Id.* It also cited specific sections supporting its position and the policy underlying it:

The requirement that safety and effectiveness for each intended use be established before introduction of the product into interstate commerce for that use came from experience showing that exclusive reliance on post-hoc remedies, such as enforcement actions for false or misleading labeling, was inadequate to protect the public health, as these remedies were not sufficient to deter manufacturers and distributors—who profit from sales of their products for any use—from making unsubstantiated and misleading claims to encourage use of their products.

Id. at 3 n.9.

68. See Brief for United States, *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012) (Nos. 09-5006-cr(L), 10-0750(CON)), 2010 WL 6351497, at *32; see also *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 203 (S.D.N.Y. 2015) ("[T]he FDA's position is that a manufacturer who markets or promotes an off-label drug risks criminal liability for 'misbranding' under 21 U.S.C. § 331(a) . . .").

69. See 21 U.S.C. § 331(a) (2012) ("The following acts and the causing thereof are hereby prohibited: (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.").

70. *Id.* § 352(f)(1)-(2).

effectiveness; the labeling on a drug approved for one use necessarily does not have adequate instructions for the new, unapproved use.⁷¹ Although the FDCA does not explicitly prohibit marketing a drug for off-label use, the FDA construes these provisions together and maintains that when a pharmaceutical sales representative promotes an off-label use, she intends to “caus[e] . . . [t]he introduction . . . into interstate commerce of [a] . . . drug . . . that is . . . misbranded” because the label does not contain “adequate directions for use.”⁷² The punishment for violation of § 331 is imprisonment for up to one year, a fine up to \$1,000, or both.⁷³

Regulations promulgated by the FDA under the authority of the FDCA⁷⁴ further this interpretation.⁷⁵ Under 21 C.F.R. § 201.128, what constitutes an intended use is based on the objective intent of the pharmaceutical company or its representatives.⁷⁶ There must be adequate labeling for the intended use on the drug’s packaging, and the FDA may infer intent from statements made by the representative.⁷⁷ Pharmaceutical sales representatives’ statements to prescribing physicians when promoting drugs play a prominent role in determining whether the representative intended to sell a misbranded drug.⁷⁸ If a sales representative makes statements to a physician about an off-label use, then his intent to introduce a misbranded drug into interstate commerce may be inferred from that statement.⁷⁹ The FDA interprets these sections of the FDCA and its

71. See *id.* § 321(p)(1) (“The term ‘new drug’ means—Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof . . .”).

72. *Id.* §§ 331(a), 352(f)(1).

73. See *id.* § 333(a)(1).

74. See *id.* § 371.

75. See, e.g., 21 C.F.R. §§ 201.5, 201.128 (2016).

76. See *id.* § 201.128.

77. See *id.* (“The words *intended uses* . . . refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.”).

78. See *id.*

79. See GUIDANCE FOR INDUSTRY, *supra* note 28, at 3-4 (“To establish a manufacturer’s or distributor’s intended use for the product, FDA is not bound by the manufacturer’s or distributor’s subjective claims of intent, but rather can present

own regulations to mean that any speech promoting off-label uses is prohibited misbranding.⁸⁰

Although pharmaceutical sales representatives are prohibited from marketing drugs off-label under FDA policy and regulations, physicians may legally prescribe drugs for unapproved uses.⁸¹ Physicians, as medical professionals, are not subject to FDA regulations.⁸² Off-label prescribing is widespread in the United States, and it may often be in the best interests of the patient.⁸³ The FDA recognizes that physicians in any particular medical specialty might consider an off-label indication to be the appropriate standard of care.⁸⁴ However, off-label prescribing can be dangerous for a patient when too little is known about how the drug works and whether it is safe or effective for a certain use.⁸⁵ For that policy

objective evidence, which may include a variety of direct and circumstantial evidence.”); *see also id.* at 4 n.12.

80. *See id.* at 4 (“Furthermore, an approved prescription drug that is intended for an unapproved use (whether referenced in labeling or not) would be considered misbranded, because the drug does not meet the regulatory exemptions from the requirement that its labeling bear ‘adequate directions for use.’” (quoting 21 U.S.C. § 352(f))).

81. *See Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000); *see also Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 200 (S.D.N.Y. 2015); Osborn, *supra* note 25, at 303.

82. *See “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices - Information Sheet*, FDA, <http://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm> [<https://perma.cc/RKR5-F6NL>] (last updated Jan. 25, 2016) (“Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.”); *see also Klasmeier & Redish*, *supra* note 15, at 316 (“[U]nder the current regulatory framework, the FDA asserts that it lacks legal authority to restrict the ability of doctors to prescribe drugs or devices for off-label uses.”).

83. *See Dresser & Frader*, *supra* note 27.

84. *See 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 (Jan. 2009), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> [<https://perma.cc/5RZF-J3WW>] (“[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals’ receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.”).

85. *See Dresser & Frader*, *supra* note 27.

reason, the FDA has not repealed or amended its prohibition against off-label promotion by pharmaceutical representatives.⁸⁶

C. Policy Arguments from Both Perspectives: The FDA and Pharmaceutical Companies

As recited in the FDCA, the purpose of the FDA is to “promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner.”⁸⁷ The FDA must, “with respect to such products, protect the public health by ensuring that . . . human . . . drugs are safe and effective.”⁸⁸ The FDCA explicitly marks out two dominant areas in which the FDA must regulate drugs: (1) reviewing and approving drug safety and efficacy after clinical trials and (2) acting to guarantee that regulated drugs are marketed in accordance with the goals of safety and efficacy.⁸⁹

Proponents of the FDA’s prohibition on off-label pharmaceutical marketing argue that the prohibition is vital to accomplishing the FDA’s purpose because it directly supports the goal of drug safety and efficacy.⁹⁰ The U.S. government has defended the FDA’s prohibition as necessary to protect the integrity of the FDA’s drug approval process.⁹¹ If pharmaceutical companies

86. The FDA maintains 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.’” *Good Reprint Practices*, *supra* note 84 (quoting 21 U.S.C. § 352(f)).

87. 21 U.S.C. § 393(b)(1) (2012).

88. *Id.* § 393(b)(2); *see also* Greene, *supra* note 23, at 240 (“[T]he very purpose of the Federal Food, Drug, and Cosmetic Act [is] to protect the public by ensuring that pharmaceutical drugs are safe and effective for their intended uses.”).

89. *See* 21 U.S.C. § 393(b)(1)-(2) (2012).

90. *See* Waxman, *supra* note 36, at 299 (“The FDCA’s restrictions on misleading and unsubstantiated promotional claims are central to its goal of preventing injury from dangerous and deceptive products. . . . As shown in a wealth of congressional documents, the history of the FDCA demonstrates beyond question that without premarket safety *and* effectiveness requirements, deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives.”).

91. Brief for United States, *supra* note 68, at *59-60 (“The statutory mechanism for achieving that critical goal [of ensuring safe and effective drugs] is the new drug approval process in 21 U.S.C. § 355. In order to obtain FDA approval, a drug manufacturer must demonstrate the safety and efficacy of a new drug for each intended use through rigorous clinical trials.”); *see also* Klasmeyer & Redish, *supra* note 15, at 316 (“[W]idespread off-label use of prescription drugs and devices conceivably undermines the FDA’s authority and deters manufacturers from seeking

could market off-label uses of drugs without obtaining FDA approval for those uses, then it “would radically undermine the incentives for manufacturers to go through the new drug approval process.”⁹² Manufacturers would not obtain supplemental new drug approval for the off-label use, which would be the equivalent of allowing manufacturers to market and sell drugs for purposes that have not been proven safe and effective, defeating the FDA’s purpose.⁹³

Additionally, proponents of the off-label marketing ban argue that it should not be interpreted as a proscription of truthful and non-misleading speech but as a preventative measure against harmful, false promotion that incidentally and necessarily prohibits some truthful speech.⁹⁴ Above all, the public policy that drives and supports the FDA’s ban is the substantial government interest in protecting consumers from unsafe and ineffective drugs.⁹⁵ The FDA attempts to prevent use of harmful drugs by ensuring that doctors do not rely on misleading promotional materials and speech from pharmaceutical sales representatives.⁹⁶

In contrast, pharmaceutical companies and other opponents who resist the FDA’s marketing restrictions argue that prescribing physicians need information on off-label uses to treat patients and that pharmaceutical companies are in the best position to provide information because they possess clinical trial results.⁹⁷ The current

on-label FDA approval for even widespread alternative uses. The fear, then, would be that the FDA’s initial approval could serve as a wedge to permit the industry’s equivalent of the Wild West, where the rule of law was seen only rarely.”).

92. Brief for United States, *supra* note 68, at *71.

93. See *id.* at *67; Greenwood, *supra* note 19, at 297.

94. See Greenwood, *supra* note 19, at 281, 297-98 (“Courts deciding commercial speech cases often repeat the refrain that false and misleading speech is entitled to no protection at all. And free speech advocates often claim that they are only concerned about a particular regulation to the extent that it applies to truthful speech. But there is no way to gain the benefits of false advertising law without sweeping in some truthful speech. . . . Given medicine’s high stakes, it is neither surprising nor unconstitutional that the prophylactic rule that governs drug claims suppresses some truthful speech.”).

95. See Waxman, *supra* note 36, at 299.

96. See Greenwood, *supra* note 19, at 291.

97. See *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 213 (S.D.N.Y. 2015) (“Such doctors . . . ‘need truthful and non-misleading information about these drugs to make informed decisions about what is best for their patients,’ but the ‘[FDA’s] current regime for regulating the flow of ‘off-label’ information to doctors about prescription drugs . . . severely restricts medical professionals’ access to information from the source most knowledgeable about the drugs: the drug manufacturers” (quoting Pl.’s Compl., *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, No. 15-cv-3588, 2015 WL 2128126, ¶ 3 (S.D.N.Y. May

regulatory regime, opponents say, “will have significant implications for the practice of medicine, the development of new drugs, and the public health,” since the flow of information from pharmaceutical companies to physicians is dammed.⁹⁸ Opponents of the FDA’s prohibition on off-label marketing also cite the fact that physicians regularly prescribe medications for unapproved uses as support for the argument that pharmaceutical representatives should be able to promote off-label.⁹⁹ Opponents of the ban assert that the impact on the public is two-fold and negative: (1) the risk that off-label drugs will harm patients exists despite the ban because physicians continue to prescribe off-label with insufficient scientific data and (2) the beneficial information that pharmaceutical companies have discovered and compiled about off-label uses cannot be shared with doctors or patients.¹⁰⁰

The conflict between opponents and proponents of the FDA’s regulatory prohibition against off-label marketing thus stems from a disagreement about how to balance the public policy interests in public health and safety with interests in freedom of speech and information.¹⁰¹ The two camps disagree about whether inconclusive or incomplete clinical data relating to off-label uses should remain in the hands of the pharmaceutical companies that commissioned the studies or whether the companies should be unregulated in their ability to use the data as promotional material.¹⁰² While the conflict has not been settled at the public policy level, courts have weighed in on the issue formulated as a First Amendment challenge to the FDA’s restriction on commercial speech.¹⁰³

II. COURTS’ VIEWS ON FIRST AMENDMENT PROTECTION FOR COMMERCIAL SPEECH

When the Supreme Court first addressed whether commercial speech is entitled to First Amendment protection, the Court

7, 2015)); Osborn, *supra* note 25, at 301 (“[T]he single greatest threat to the pharmaceutical industry may be the policy environment within the United States, which is restricting the ability of companies to speak truthfully with physicians about their products.”).

98. See Osborn, *supra* note 25, at 303.

99. See *id.* at 303-05.

100. See Klasmeier & Redish, *supra* note 15, at 316.

101. See *infra* Section I.C.

102. See *infra* Section I.C.

103. See *infra* Parts II and III.

determined that commercial speech did not merit protection because the value of the speech was so low compared to political or other public discourse.¹⁰⁴ Over time, proponents of commercial speech spoke out against the Supreme Court's decision.¹⁰⁵ Now, courts afford commercial speech an intermediate level of protection, and restrictions on commercial speech are analyzed under a four-factor test that the Supreme Court crafted in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*.¹⁰⁶

A. The Early History of First Amendment Protection for Commercial Speech

The Supreme Court first considered whether the First Amendment protects commercial speech in 1942, in *Valentine v. Chrestensen*.¹⁰⁷ In *Chrestensen*, the Court upheld a New York City ordinance that prohibited distribution of commercial advertising handouts in public streets but that allowed distribution of informational or political handouts.¹⁰⁸ In the decades following *Chrestensen*, legal scholars criticized the decision for denying protection to commercial speech.¹⁰⁹ For example, Professor Martin Redish argued in 1971 that commercial speech should be afforded First Amendment protection based on its social value.¹¹⁰ Redish

104. See *infra* Section II.A.

105. See *infra* Section II.A.

106. See *infra* Section II.B.

107. See 316 U.S. 52, 54 (1942).

108. See *id.* at 53, 55 (“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 *N.Y. Times Co. v. Sullivan*, 376 U.S. 254, 265-66 (1964) (reiterating that the Court distinguished between distribution of “information and . . . opinion” and “purely commercial advertising” in *Valentine v. Chrestensen* for First Amendment purposes).

109. See, e.g., George K. Gardner, *Free Speech in Public Places*, 36 B.U. L. REV. 239, 246 (1956) (finding that “[t]he opinion which the Court offers in support of [*Chrestensen*] can be justified only on the theory that the constitution values freedom of political propaganda more highly than it values the freedom to organize cooperation by means of trade,” but arguing that the Constitution protects commercial speech no less than religious, scientific, informative, or political speech); see also Martin H. Redish, *The First Amendment in the Marketplace: Commercial Speech and the Values of Free Expression*, 39 GEO. WASH. L. REV. 429, 432 (1971). But see Thomas I. Emerson, *Toward a General Theory of the First Amendment*, 72 YALE L.J. 877, 956 (1963) (generally approving of the Supreme Court's view of commercial speech in *Chrestensen* because of its relation to property rights rather than free expression).

110. See Redish, *supra* note 109, at 432.

contended that consumers benefit when provided with information about products because only then can they make knowledgeable, economically efficient decisions.¹¹¹ However, the Supreme Court adhered to the holding in *Chrestensen* until the mid-1970s.¹¹²

In 1975, the Court extended First Amendment protection to commercial speech under *Bigelow v. Virginia*.¹¹³ It acknowledged *Chrestensen*, but it characterized the holding in that case as “distinctly a limited one” that did not apply to all commercial advertising.¹¹⁴ The *Bigelow* Court corrected what it viewed as a misapprehension that advertising and other commercial speech were not entitled to First Amendment protection,¹¹⁵ holding instead that commercial speech merits some level of constitutional safeguarding.¹¹⁶ Specifically, the Court cited the informative nature of the advertisement under consideration¹¹⁷ as the interest that

111. See *id.* at 433 (“If the individual is to achieve the maximum degree of material satisfaction permitted by his resources, he must be presented with as much information as possible concerning the relative merits of competing products.”).

112. See, e.g., *Head v. N.M. Bd. of Exam’rs in Optometry*, 374 U.S. 424, 432 n.12 (1963) (declining to consider whether a state law prohibiting optometry advertisements violated the First Amendment); see also, e.g., *Pittsburgh Press Co. v. Pittsburgh Comm’n on Human Relations*, 413 U.S. 376, 388 (1973) (declining to address the argument that “commercial speech should be accorded a higher level of protection than *Chrestensen* and its progeny would suggest” and declining to “abrogate the distinction between commercial and other speech”).

113. *Bigelow v. Virginia*, 421 U.S. 809, 818 (1975).

114. *Id.* at 819-20. The Court did not overrule *Chrestensen* but indicated that the First Amendment protects commercial speech in some situations, stating:

[T]he holding [of *Chrestensen*] is distinctly a limited one: the ordinance was upheld as a reasonable regulation of the manner in which commercial advertising could be distributed. The fact that it had the effect of banning a particular handbill does not mean that *Chrestensen* is authority for the proposition that all statutes regulating commercial advertising are immune from constitutional challenge. The case obviously does not support any sweeping proposition that advertising is unprotected *per se*.

Id.

115. *Id.* at 819-20, 825.

116. *Id.* at 826 (“Advertising is not . . . stripped of all First Amendment protection. The relationship of speech to the marketplace of products or of services does not make it valueless in the marketplace of ideas.”).

117. *Id.* at 821-22. The advertisement offered assistance in seeking a legal abortion in New York to people in Virginia, *id.* at 812, and in the Court’s view:

[It] did more than simply propose a commercial transaction. It contained factual material of clear “public interest.” Portions of its message, most prominently the lines, “Abortions are now legal in New York. There are no residency requirements,” involve the exercise of the freedom of communicating information and disseminating opinion. Viewed in its

warranted First Amendment protection.¹¹⁸ The Court advanced a balancing test, weighing the government interest in regulating speech against the First Amendment interest, as the method by which to determine whether specific speech is protected.¹¹⁹ One year later, in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, the Court reaffirmed *Bigelow* and made definitively clear that commercial speech is “not ‘wholly outside the protection of the First Amendment.’”¹²⁰ The Court effectively brought commercial speech within the realm of First Amendment jurisprudence through *Bigelow* and *Virginia State Board*,¹²¹ but it soon redefined the test used to analyze restrictions on commercial speech.¹²²

B. The *Central Hudson* Four-Factor Test for Laws Restricting Commercial Speech

In 1980, the Court again addressed protection of commercial speech.¹²³ In *Central Hudson Gas v. Public Service Commission of New York*, an electrical utility company sued the Public Service Commission of New York, alleging that its ban on promotional advertising for electrical utilities violated the First Amendment.¹²⁴ The Commission argued that the ban conserved energy by preventing electricity companies from encouraging energy consumption.¹²⁵ Contrary to the decisions of the state courts below,¹²⁶ the U.S. Supreme Court held that the ban violated the First and Fourteenth Amendments.¹²⁷ Justice Powell, writing for the Court, emphasized that commercial speech derives First Amendment protection from its

entirety, the advertisement conveyed information of potential interest and value to a diverse audience.

Id. at 822.

118. *Id.* at 821-22.

119. *Id.* at 826.

120. *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 776 (1976) (Stewart, J., concurring).

121. *See Bigelow*, 421 U.S. at 825; *see also Va. State Bd. of Pharmacy*, 425 U.S. at 770.

122. *See infra* Section II.B for a discussion of the *Central Hudson* test for commercial speech.

123. *See Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 558 (1980).

124. *Id.* at 558-59.

125. *Id.* at 558-60.

126. *Id.* at 560-61.

127. *Id.* at 561, 571-72.

role in ensuring free circulation of information.¹²⁸ “Consequently,” the Court stated, “there can be no constitutional objection to the suppression of commercial messages that do not accurately inform the public about lawful activity. The government may ban forms of communication more likely to deceive the public than to inform it or commercial speech related to illegal activity.”¹²⁹ In the Court’s view, then, only some commercial speech merits First Amendment protection.¹³⁰

The Court developed a four-factor test to determine whether a law that restricts commercial speech violates the First Amendment’s guarantee of freedom of speech.¹³¹ First, a court must consider whether the First Amendment protects the speech; to merit protection initially, the speech must concern lawful activity and must not be misleading.¹³² Second, a court must consider whether the government interest asserted as justification for the restriction is substantial.¹³³ Third, a court must consider “whether the regulation directly advances the governmental interest asserted.”¹³⁴ Fourth, a court must consider whether the regulation is only as extensive as necessary to achieve the interest.¹³⁵ This test resembles intermediate scrutiny, a

128. *Id.* at 561-63 (“Commercial expression not only serves the economic interest of the speaker, but also assists consumers and furthers the societal interest in the fullest possible dissemination of information. . . . The First Amendment’s concern for commercial speech is based on the informational function of advertising.”).

129. *Id.* at 563-64.

130. *Id.* at 562-64.

131. *Id.* at 564-66.

132. *Id.* at 566.

133. *Id.*

134. *Id.*

135. *Id.* The *Central Hudson* Court phrased the fourth factor of the inquiry as “whether [the regulation] is not more extensive than is necessary to serve that interest.” *Id.* As to the first step, the *Central Hudson* Court ruled that advertising for electrical utilities is commercial speech protected by the First Amendment because it is neither “deceptive [n]or related to unlawful activity.” *Id.* at 566-68, 566 n.9. In the second step of the analysis, the Court found that the government’s interests in energy conservation and ensuring fair, efficient utility rates were substantial. *Id.* at 568-69. In the third step, the Court found that the ban on electrical utility advertising directly advanced the government’s interest in energy conservation because of the “immediate connection between advertising and demand for electricity.” *Id.* at 569. However, the Court found that the ban was more restrictive than necessary to further the government’s interest in energy conservation because the ban also prohibited advertising that would promote alternative, more efficient modes of consumption. *See id.* at 569-70. Therefore, the Court held that the Public Service Commission’s

standard of review more deferential to the government than strict scrutiny, because commercial speech is less valuable than other types of pure speech.¹³⁶

In 1989, the Court clarified the parameters of the fourth step of the *Central Hudson* analysis in *Board of Trustees of the State University of New York v. Fox*.¹³⁷ The Court declared that the government need not choose the least restrictive means to preserve its interests for a challenged regulation to be “only as extensive as necessary.”¹³⁸ Rather, the Court rejected that strict interpretation of “necessary” and stated that *Central Hudson* “requires something short of a least-restrictive-means standard.”¹³⁹ The fit between the means and the ends of the regulation must only be a “reasonable” fit.¹⁴⁰ The Court based this decision on the grounds that commercial speech merits less protection than other types of speech.¹⁴¹

Today, *Central Hudson*’s four-factor test defines commercial speech doctrine and limits the government’s ability to restrict commercial speech.¹⁴² Commercial speech is considered a low-value

moratorium on electrical-utility advertising violated the First Amendment because it was too restrictive. *See id.* at 571-72.

136. *See id.* at 562-63 (“The Constitution . . . accords a lesser protection to commercial speech than to other constitutionally guaranteed expression.”); *see also* Ashutosh Bhagwat, *The Test That Ate Everything: Intermediate Scrutiny in First Amendment Jurisprudence*, 2007 U. ILL. L. REV. 783, 794 (2007) (“Commercial speech regulations, however, may be, and generally are, content-based, but because of the lower constitutional value of such speech, only intermediate scrutiny applies.”).

137. *See Bd. of Trs. of State Univ. of N.Y. v. Fox*, 492 U.S. 469, 476-77 (1989).

138. *See id.*

139. *Id.* at 477.

140. *See id.* at 480 (“What our decisions require is a “fit” between the legislature’s ends and the means chosen to accomplish those ends, a fit that is not necessarily perfect, but reasonable; that represents not necessarily the single best disposition but one whose scope is ‘in proportion to the interest served,’ that employs not necessarily the least restrictive means but, as we have put it in the other contexts discussed above, a means narrowly tailored to achieve the desired objective. Within those bounds we leave it to governmental decisionmakers to judge what manner of regulation may best be employed.” (quoting *Posadas de Puerto Rico Assoc. v. Tourism Co.*, 478 U.S. 328, 341 (1986); *In re R.M.J.*, 455 U.S. 191, 203 (1982))).

141. *See id.* at 477 (“Our jurisprudence has emphasized that ‘commercial speech [enjoys] a limited measure of protection, commensurate with its subordinate position in the scale of First Amendment values,’ and is subject to ‘modes of regulation that might be impermissible in the realm of noncommercial expression.’” (quoting *Ohralik v. Ohio State Bar Ass’n*, 436 U.S. 447, 456 (1978))).

142. *See supra* text accompanying notes 131-36.

type of speech, yet *Central Hudson* is only slightly deferential to the government.¹⁴³ When the Second Circuit first applied *Central Hudson* to the FDA's prohibition on off-label pharmaceutical promotion, it came out in favor of commercial speech over drug regulation.¹⁴⁴

III. COURTS' VIEWS ON FIRST AMENDMENT PROTECTION FOR OFF-LABEL PROMOTION

The Second Circuit and the U.S. District Court for the Southern District of New York have both addressed issues regarding pharmaceutical companies' off-label promotion of drugs.¹⁴⁵ The Second Circuit found that the FDA's prohibition on off-label marketing violated the First Amendment under the *Central Hudson* analysis for commercial speech.¹⁴⁶ Following the Second Circuit, the Southern District of New York permitted a pharmaceutical company to promote a drug off-label using truthful and non-misleading speech.¹⁴⁷

A. *United States v. Caronia*: The Second Circuit Debates the Off-Label Marketing Ban

In *United States v. Caronia*, the Second Circuit addressed whether the FDA's policy of prohibiting pharmaceutical sales representatives from marketing off-label uses of drugs violated the First Amendment.¹⁴⁸ Alfred Caronia, a pharmaceutical sales representative, was prosecuted for conspiring "to introduce a misbranded drug into interstate commerce,"¹⁴⁹ a prohibited act under the FDCA.¹⁵⁰ Caronia had been hired specifically to promote the drug Xyrem, which the FDA approved to treat patients with narcolepsy who experienced either cataplexy or excessive daytime sleepiness.¹⁵¹

143. See *supra* text accompanying note 136.

144. See *infra* Part III.

145. See *infra* Sections III.A-B.

146. See *infra* Section III.A.

147. See *infra* Section III.B.

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

149. *Id.*

150. See *supra* Section I.B.

151. See *Caronia*, 703 F.3d at 155-56; see also *Xyrem*, JAZZ PHARMACEUTICALS, https://www.xyrem.com/?gclid=CjwKEAjwh8exBRDyyqqH9pvf1ncSJAu40E3cfCdAd2-Cai3N0YLrMRM3zfn7ogK8iDrh0aGraAGOhoCRevw_wcB [https://perma.cc/DDE8-SXL7] (last visited Nov. 17, 2016) ("Xyrem is a prescription

The FDA categorized Xyrem as a Schedule III controlled substance,¹⁵² a category of drugs that have a moderate to high potential for abuse and an accepted medical use in the United States.¹⁵³ The drug information label contains a warning that Xyrem is a central nervous system depressant and that abuse can cause “adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.”¹⁵⁴ Despite Xyrem’s risks, Caronia promoted the drug to a physician for unapproved uses in a conversation captured in an audio recording.¹⁵⁵ Caronia indicated that although Xyrem was only approved for cataplexy and excessive daytime sleepiness, “it’s going to insomnia, Fibromyalgia[,] periodic leg movement, restless leg . . . Parkinson’s and . . . other sleep disorders are underway such as MS,” uses for which Xyrem had not been approved.¹⁵⁶

Before and at trial, Caronia argued that the government was prosecuting him for promotional speech that was protected by the First Amendment.¹⁵⁷ The government argued, however, that it prosecuted Caronia “for the unlawful conduct of misbranding and conspiring to misbrand a drug and not for his promotional speech, the latter of which . . . only constituted proof of Xyrem’s intended use.”¹⁵⁸ The district court agreed that the government was prosecuting Caronia for promotional speech rather than conduct, but it found that the regulation of commercial speech did not violate the First Amendment.¹⁵⁹ The jury found Caronia guilty of conspiring to misbrand.¹⁶⁰

medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy): suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)[;] excessive daytime sleepiness (EDS) in people who have narcolepsy.”).

152. See JAZZ PHARM., HIGHLIGHTS OF PRESCRIBING INFORMATION 1 (Sept. 2016) [hereinafter XYREM PRESCRIBING INFORMATION], <http://pp.jazzpharma.com/pi/xyrem.en.USPI.pdf> [<https://perma.cc/8AYT-3WV2>].

153. See Controlled Substances Act, Pub. L. No. 91-513, § 202(b)(3)(A)-(B), 84 Stat. 1236, 1247 (1970) (codified at 21 U.S.C. § 812(b)(3)(A)-(B) (2012)).

154. XYREM PRESCRIBING INFORMATION, *supra* note 152, at 3.

155. See *Caronia*, 703 F.3d at 156.

156. *Id.*

157. See *id.* at 158.

158. *Id.* (citing *United States v. Caronia*, 576 F. Supp. 2d 385, 394-95 (E.D.N.Y. 2008)).

159. See *id.* (citing *Caronia*, 576 F. Supp. 2d at 395, 401-02).

160. See *id.* at 159.

On appeal, the Second Circuit reviewed Caronia's First Amendment claim *de novo*.¹⁶¹ First, based on the principle of constitutional avoidance, the court concluded that the FDCA and FDA regulations do not prohibit off-label marketing "because such a construction would raise First Amendment concerns."¹⁶² Yet, like the district court, the Second Circuit found that the government had indeed prosecuted Caronia for his promotional speech under the FDCA provisions.¹⁶³ The court refused to accept the government's argument that it used Caronia's speech only as evidence of intent to misbrand, rather than that it identified the speech itself as prohibited.¹⁶⁴

Finding that the government prosecuted Caronia for his promotional speech, the Second Circuit held that the prosecution violated the First Amendment, and the court vacated Caronia's conviction.¹⁶⁵ The court presented an assessment of First Amendment doctrine and drew incompatible conclusions about which standard of scrutiny to apply to the FDA's restriction on off-label marketing.¹⁶⁶ First, the court concluded that strict scrutiny applied because the speech prohibition was both content-based and speaker-based.¹⁶⁷ Second, and despite its first conclusion, the Second Circuit proceeded to apply the form of intermediate scrutiny created in *Central Hudson* for commercial speech,¹⁶⁸ concluding "that the 'outcome is the same whether a special commercial speech inquiry

161. See *id.* at 160 (citing *Conn. Bar Ass'n v. United States*, 620 F.3d 81, 89 (2d Cir. 2010)).

162. *Id.*; see *id.* (noting that "[w]hile the FDCA makes it a crime to misbrand or conspire to misbrand a drug, the statute and its accompanying regulations do not expressly prohibit or criminalize off-label promotion. Rather, the FDCA and FDA regulations reference 'promotion' only as evidence of a drug's intended use" (citations omitted)).

163. See *id.*

164. See *id.* at 160-61.

165. *Id.* at 162, 169.

166. *Id.* at 163-64.

167. *Id.* at 163 (citing the United States Supreme Court's decision in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011)). Application of the Supreme Court's holding in *Sorrell* to the facts of *Caronia* is inapposite because the issue in *Sorrell* addressed a state law that "restricts the sale, disclosure, and use of pharmacy records that reveal the prescribing practices of individual doctors," *Sorrell*, 131 S. Ct. at 2659, rather than off-label pharmaceutical marketing. For an analysis of commercial speech as content-based and speaker-based, see Robert Post, *The Constitutional Status of Commercial Speech*, 48 UCLA L. REV. 1, 5-6 (2000), in which Post describes the frustration of attempting to characterize commercial speech based on the speaker or the content, since at times it can be characterized by both and neither.

168. See *supra* Section II.B.

or a stricter form of judicial scrutiny is applied.”¹⁶⁹ Under either method, the court found that the government’s prosecution of Caronia for his speech failed heightened scrutiny.¹⁷⁰

Proceeding through the four-factor *Central Hudson* analysis,¹⁷¹ the Second Circuit found under the first prong that Caronia’s commercial speech merited First Amendment protection because it discussed off-label drug use, a lawful activity, and because “promotion of off-label drug use is not in and of itself false or misleading.”¹⁷² However, the court noted that the government did not argue in its brief that Caronia’s speech was about unlawful activity or that it was false or misleading.¹⁷³ Under the second prong, the court found that the government’s interests in protecting safety, health, and the integrity of the regulatory drug approval process were substantial interests.¹⁷⁴ The court gave in-depth consideration to the government’s theory of prosecution under the third and fourth prongs.¹⁷⁵

Central Hudson’s third prong examines whether the government regulation or action directly advances the government’s asserted interests.¹⁷⁶ The court reasoned that the government’s view of the FDCA as prohibiting off-label promotion does not further its interests in protecting the public or in preserving the integrity of the FDA drug approval process because physicians can legally prescribe drugs to patients for off-label uses.¹⁷⁷ The court criticized the regulations for being speaker-based, since only pharmaceutical

169. *Caronia*, 703 F.3d at 164 (quoting *Sorrell*, 131 S. Ct. at 2667). See *infra* Part IV for an argument that the FDA’s prohibition on off-label marketing survives intermediate scrutiny under *Central Hudson*.

170. *Caronia*, 703 F.3d at 164-69.

171. See *supra* Section II.B.

172. *Caronia*, 703 F.3d at 165.

173. *Id.* at 165 n.10.

174. *Id.* at 166 (“Second, the government’s asserted interests in drug safety and public health are substantial. Specifically, the government asserts an interest in preserving the effectiveness and integrity of the FDCA’s drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs.”).

175. *Id.* at 166-69.

176. See *supra* text accompanying note 134.

177. *Caronia*, 703 F.3d at 166 (“In effect, even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use, drugs for off-label purposes. As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government’s goals of preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs.”).

manufacturers and representatives are contemplated by the FDA's ban.¹⁷⁸ Additionally, the court reasoned that the prohibition actually harms patients who would benefit if their physicians could get pertinent information on off-label uses from pharmaceutical companies.¹⁷⁹ Based on its conclusions under the first prong that off-label promotion is not inherently false or misleading¹⁸⁰ and that Caronia's promotional speech was not false or misleading, the court asserted that the free flow of information about off-label uses could only be beneficial.¹⁸¹

Central Hudson's fourth prong examines whether the regulation is only as extensive as necessary to achieve the interest.¹⁸² As to this inquiry, the *Caronia* court found that the absolute, criminal prohibition against off-label marketing was more extensive than necessary to achieve the government's interests.¹⁸³ The court grounded its conclusion on the perceived availability of feasible alternatives for implementation by the FDA, such as teaching physicians to distinguish true from false or misleading speech, developing warning systems and safety schedules for off-label uses, requiring registration of all intended uses upon granting initial approval, and capping the number of issuable off-label prescriptions.¹⁸⁴

Under a *Central Hudson* analysis, the court found that the FDA's prosecution of Caronia under the FDCA for truthful, non-misleading speech violated the First Amendment.¹⁸⁵ The court also found that the FDA's interpretation of the FDCA did not directly advance the government's interests and was more extensive than necessary to achieve the interests.¹⁸⁶ Rather, the Second Circuit held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the

178. *Id.*

179. *Id.* ("[P]rohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.")

180. *See supra* text accompanying note 172.

181. *Caronia*, 703 F.3d at 167.

182. *See supra* text accompanying notes 135, 137-41.

183. *Caronia*, 703 F.3d at 167.

184. *Id.* at 168.

185. *Id.* at 166-68.

186. *Id.*

lawful, off-label use of an FDA-approved drug.”¹⁸⁷ Recently, the District Court for the Southern District of New York followed the Second Circuit in its holding.¹⁸⁸

B. *Amarin Pharma, Inc. v. U.S. Food & Drug Administration: An Extension of Caronia*

In August of 2015, in *Amarin Pharma, Inc. v. U.S. Food and Drug Administration*, the District Court for the Southern District of New York applied and extended the Second Circuit’s holding in *Caronia* when it granted a preliminary injunction to Amarin, the plaintiff–pharmaceutical company, to prevent the FDA from following through with threats to prosecute Amarin for misbranding.¹⁸⁹ The FDA had approved Amarin’s drug Vascepa to treat patients with high triglyceride levels¹⁹⁰ at risk for pancreatitis and cardiovascular disease,¹⁹¹ but it rejected Amarin’s supplemental new drug application for approval of Vascepa for a second use: reducing the risk of cardiovascular disease in patients with *persistently* high triglyceride levels.¹⁹² The FDA responded that Amarin’s clinical trials were inconclusive about the benefits of the drug for the second use.¹⁹³ Although Amarin’s study revealed that Vascepa effectively reduced triglycerides in patients with persistently high levels, the FDA found that Amarin’s study did not prove a direct correlation between lower triglyceride levels and reduced risk of cardiovascular disease.¹⁹⁴ In a final response letter to Amarin, the FDA warned that Vascepa “may be considered to be misbranded under the [FDCA]” if Amarin marketed Vascepa for use

187. *Id.* at 169.

188. *See infra* Section III.B.

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

190. Triglycerides are defined as “any of a group of lipids that are esters formed from one molecule of glycerol and three molecules of one or more fatty acids, are widespread in adipose tissue, and commonly circulate in the blood in the form of lipoproteins—called also *neutral fat*.” *Triglyceride*, MERRIAM-WEBSTER MED. DICTIONARY, <http://c.merriam-webster.com/medlineplus/triglyceride> [<https://perma.cc/HLD3-FC3P>] (last visited Nov. 17, 2016).

191. *See Amarin*, 119 F. Supp. 3d at 209.

192. *Id.* at 210-12.

193. *Id.* at 211-12.

194. *Id.*

in patients with persistently high levels using the results of the inconclusive study.¹⁹⁵

After the FDA rejected Amarin's supplemental new drug application, Amarin filed a complaint against the FDA, arguing that the FDA's ban on off-label marketing and its threatened prosecution for misbranding violated the First Amendment.¹⁹⁶ Amarin alleged that it wanted to market Vascepa using truthful and non-misleading statements based on the results of its clinical trials.¹⁹⁷ Amarin's suggested marketing materials included three specific statements about Vascepa's efficacy in lowering triglyceride levels and about the results of Amarin's recent clinical study, a summary of the results of the study, peer-reviewed scientific articles relating to the medical field, and disclosure statements about Vascepa's off-label status and possible effect on cardiovascular disease.¹⁹⁸ Based on the factual, unbiased, and academic nature of the statements and materials Amarin proposed to use promotionally, the court granted Amarin preliminary relief, declaring that "Amarin may engage in truthful and non-misleading speech promoting the off-label use of Vascepa . . . and under *Caronia*, such speech may not form the basis of a prosecution for misbranding."¹⁹⁹ The district court's ruling in favor of Amarin reinforced the Second Circuit's decision in *Caronia* that under the First Amendment the FDA cannot prevent pharmaceutical manufacturers from making truthful, non-misleading statements about off-label drugs.²⁰⁰

After the courts' decisions in *Caronia* and *Amarin*, it is unclear to what extent the FDA's prohibition against off-label marketing by pharmaceutical companies retains any force.²⁰¹ The *Caronia* court

195. *Id.* at 212.

196. *Id.*

197. *Id.* Amarin attached its suggested marketing statements as exhibits to the complaint, but the FDA did not have an opportunity to review the statements before Amarin filed suit. *Id.* at 215-16.

198. *Id.* at 214-15.

199. *Id.* at 237.

200. *Id.* at 224 ("In light of the parties' conflicting readings of *Caronia* and the FDA's position that it may bring a misbranding action against a manufacturer based solely on truthful and non-misleading speech evincing the intent to promote an off-label use, the Court has closely reviewed *Caronia*. The Court's considered and firm view is that, under *Caronia*, the FDA may *not* bring such an action based on truthful promotional speech alone, consistent with the First Amendment. A fair reading of that decision refutes the FDA's view that the Second Circuit's ruling was limited to the facts of *Caronia*'s particular case.").

201. Although the Second Circuit held that the FDA's ban violates the First Amendment, other circuits have declined to follow that holding. See, for example,

declined to construe the FDCA and FDA regulations to prohibit off-label promotion, instead choosing to decide whether prosecution for off-label marketing violates the First Amendment.²⁰² Using the *Central Hudson* test for restrictions on commercial speech, the Second Circuit held that such prosecution was unconstitutional.²⁰³ The *Amarin* court affirmed and clarified *Caronia*'s holding, asserting that the FDA could not criminalize truthful, non-misleading off-label promotion.²⁰⁴

IV. IN DEFENSE OF THE BAN ON OFF-LABEL PROMOTION: PERMITTING SOME COMMERCIAL SPEECH ON OFF-LABEL USES IS A SOLUTION

Although the *Caronia* and *Amarin* courts found the FDA's ban to be unconstitutional,²⁰⁵ the *Caronia* court misapplied the four-factor *Central Hudson* test and erroneously found that the FDA's prohibition on off-label marketing violates the First Amendment.²⁰⁶ Contrary to the *Caronia* and *Amarin* courts' findings, the FDA's ban

Ramirez v. Medtronic Inc., 961 F. Supp. 2d 977, 990 n.8 (D. Ariz. 2013), in which the United States District Court for the District of Arizona stated:

The Court recognizes that the Second Circuit has determined that a prohibition on off-label promotion can raise First Amendment concerns. *United States v. Caronia*, 703 F.3d 149, 160-69 (2d Cir. 2012). The Ninth Circuit, however, has assumed that off-label promotion does violate federal law. *Carson v. Depuy Spine, Inc.*, 365 [F. App'x] 812, 815 (9th Cir. 2010). Medtronic has not directly attacked the constitutionality of such a ban in this preliminary proceeding, and the Court therefore assumes for purposes of this Motion that the ban on off-label promotion remains constitutionally viable.

Id. Therefore, the constitutionality of the FDA's ban remains contested. *See id.*

202. *United States v. Caronia*, 703 F.3d 149, 168-69 (2d Cir. 2012) (“[E]ven if speech can be used as evidence of a drug’s intended use, we decline to adopt the government’s construction of the FDCA’s misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs. . . . 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.”).

203. *Id.*

204. *Amarin*, 119 F. Supp. 3d at 237 (“Specifically the Court declares that . . . *Amarin* may engage in truthful and non-misleading speech promoting the off-label use of Vascepa, *i.e.*, to treat patients with persistently high triglycerides, and under *Caronia*, such speech may not form the basis of a prosecution for misbranding . . .”).

205. *See supra* Part III.

206. *See infra* Section IV.A.

meets the requirements of *Central Hudson* for a governmental restriction on commercial speech because speech promoting the introduction of misbranded drugs into interstate commerce is not protected speech.²⁰⁷ Despite the constitutionality of the ban, a conflict remains between the FDA's and pharmaceutical companies' competing interests.²⁰⁸ The solution to the informational deadlock that results from the ban is to allow pharmaceutical companies to generate and disseminate factual, unbiased statements about off-label uses of drugs based on the results of clinical trials.²⁰⁹

A. The *Caronia* Court's Mistake: The First Amendment Does Not Protect Off-Label Promotion

In *United States v. Caronia*, the Second Circuit incorrectly applied the *Central Hudson* analysis for commercial speech to the FDA's prohibition against off-label marketing by pharmaceutical sales representatives.²¹⁰ As an initial matter, the court erroneously applied a standard of review that more closely resembled strict scrutiny than intermediate scrutiny.²¹¹ Under *Central Hudson*,²¹² any law restricting commercial speech must be scrutinized under the four-prong analysis that resembles intermediate scrutiny.²¹³ The Second Circuit, however, took into consideration the fact that the FDA's regulation was content-based and speaker-based,²¹⁴ which led it to use a standard of review closer to strict scrutiny.²¹⁵

207. See *infra* Section IV.A.

208. See *infra* Section IV.B.

209. See *infra* Section IV.B.

210. See *supra* Sections II.B, III.A.

211. See *United States v. Caronia*, 703 F.3d 149, 164-65 (2d Cir. 2012) ("The government's construction of the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers is content- and speaker-based, and, therefore, subject to heightened scrutiny."); see also *supra* notes 167-69 and accompanying text.

212. See *supra* Section II.B.

213. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 562-63 (1980) ("The Constitution therefore accords a lesser protection to commercial speech than to other constitutionally guaranteed expression. . . . The protection available for particular commercial expression turns on the nature both of the expression and of the governmental interests served by its regulation."); see *supra* text accompanying notes 131-36.

214. *Caronia*, 703 F.3d at 166 ("As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of

Under contemporary First Amendment commercial speech doctrine, it is irrelevant whether the restriction is content-based or speaker-based because commercial speech is necessarily characterized both by its content and by its speaker, and therefore any restriction will also be based on those characteristics.²¹⁶ Any restriction on commercial speech is speaker-based: The restriction will affect only those seeking to sell something in the market, whether a product or the speech itself, because otherwise the speech would not be characterized as commercial.²¹⁷ Any restriction on commercial speech is also content-based: The restriction will affect only speech that engages in “commercial advertising [or] . . . ‘propose[s] a commercial transaction’” because otherwise the speech would not be characterized as commercial.²¹⁸ The Supreme Court took these realities into account when crafting the *Central Hudson* analysis for restrictions on commercial speech,²¹⁹ and the Court concluded that despite its discriminatory nature, commercial speech would be analyzed under intermediate scrutiny²²⁰ because of its “lower constitutional value” compared to other speech.²²¹

preserving the efficacy and integrity of the FDA’s drug approval process and reducing patient exposure to unsafe and ineffective drugs.”).

215. *Id.* at 163 (“Content-based speech restrictions are subject to ‘strict scrutiny’—that is, the government must show that the regulation at issue is narrowly tailored to serve or promote a compelling government interest. . . . Meanwhile, non-content-based regulation and regulation of commercial speech—expression solely related to the economic interests of the speaker and its audience—are subject to intermediate scrutiny.”).

216. *See* Bhagwat, *supra* note 136, at 794 (“Commercial speech regulations, however, may be, and generally are, content-based, but because of the lower constitutional value of such speech, only intermediate scrutiny applies.”). *Cf.* Post, *supra* note 167, at 5-6 (explaining the difficulty in characterizing commercial speech based on the speaker or the content, since at times it can be characterized by both and neither).

217. *Cf.* Post, *supra* note 167, at 7-8 (arguing that commercial speech should not be defined based on its characteristics as content- or speaker-based, but rather that commercial speech should be awarded First Amendment protection based on its contribution to public discourse, which has constitutional value because it allows for participation in democracy).

218. *See* Bhagwat, *supra* note 136, at 793-95 (citing *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 367 (2002)) (comparing content-based and content-neutral speech regulations).

219. *See supra* Sections II.A, II.B.

220. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 573 (1980) (Blackmun, J., concurring) (“The Court asserts that ‘a four-part analysis has developed’ from our decisions concerning commercial speech. Under this four-part test a restraint on commercial ‘communication [that] is neither misleading nor related to unlawful activity’ is subject to an intermediate level of scrutiny, and

Although the *Caronia* court ultimately proceeded to apply the four-factor form of intermediate scrutiny under *Central Hudson*, consideration of the strict scrutiny standard of review influenced how rigorously the court critiqued the FDA's choice of regulation.²²² For example, under the third prong, the court considered the fact that the prohibition was speaker-based and found that such a discriminatory regulation did not directly advance the interests of the government.²²³ The court's emphasis on the speaker-based nature of the restriction²²⁴ demonstrates that it gave less deference to the government than is required by the *Central Hudson* intermediate scrutiny test.²²⁵

1. *The Caronia Court's Incorrect Application of the First Central Hudson Factor*

Under the first step of the *Central Hudson* test, the Second Circuit concluded that the First Amendment protected *Caronia*'s commercial speech because (1) off-label promotion by pharmaceutical companies is not inherently false or misleading and (2) the speech contained information about off-label drug use, which is a lawful activity.²²⁶ The conclusion that off-label promotion is not inherently misleading misrepresents the thrust of the first *Central Hudson* factor: Although it may be true that off-label promotion is not inherently false or misleading, the question under *Central Hudson* is not whether a broad category of commercial speech is inherently false or misleading, but rather whether the commercial

suppression is permitted whenever it 'directly advances' a 'substantial' governmental interest and is 'not more extensive than is necessary to serve that interest.' I agree with the Court that this level of intermediate scrutiny is appropriate for a restraint on commercial speech designed to protect consumers from misleading or coercive speech, or a regulation related to the time, place, or manner of commercial speech.").

221. Bhagwat, *supra* note 136, at 794.

222. See *United States v. Caronia*, 703 F.3d 149, 165-67 (2d Cir. 2012).

223. *Id.* at 166 ("In effect, even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use, drugs for off-label purposes. As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs." (emphasis added)).

224. *Id.*

225. *Cent. Hudson*, 447 U.S. at 573 (Blackmun, J., concurring).

226. *Caronia*, 703 F.3d at 165.

speech is “more likely to deceive the public than to inform it.”²²⁷ Speech that is inherently false or misleading would never come under the purview of *Central Hudson* because such speech is not informative; the only reason the First Amendment protects commercial speech is to preserve its informative function.²²⁸ Rather, Justice Powell’s statement in *Central Hudson* that “[t]he government may ban forms of communication more likely to deceive the public than to inform it” implies a balancing test to determine whether the regulated speech could be reasonably expected to be false or misleading.²²⁹

In *Caronia*, the court should have examined whether off-label pharmaceutical promotion by sales representatives is “more likely to deceive [physicians] than to inform [them].”²³⁰ One public policy that supports the ban on off-label promotion—and one of the overarching goals of the FDCA—is to protect public health and safety by preventing doctors from relying on promotional materials with false claims or misleading information about a drug’s uses and efficacy.²³¹ The FDCA, the FDA’s statutory mandate, requires the FDA to review clinical trials before approving drugs as safe and effective, and to regulate drug marketing for the same purpose.²³² This mandate demonstrates that Congress believed that before clinical trials are complete, there is insufficient information to prove that the drugs will not harm the public.²³³ Although not all off-label promotion is

227. *Cent. Hudson*, 447 U.S. at 563 (“The First Amendment’s concern for commercial speech is based on the informational function of advertising. Consequently, there can be no constitutional objection to the suppression of commercial messages that do not accurately inform the public about lawful activity.” (citations omitted)).

228. *Id.* at 561-63 (“Commercial expression not only serves the economic interest of the speaker, but also assists consumers and furthers the societal interest in the fullest possible dissemination of information. . . . The First Amendment’s concern for commercial speech is based on the informational function of advertising.”).

229. *Id.* at 563.

230. *Id.*

231. 21 U.S.C. § 393(b)(1)-(2) (2012); *see also* Greene, *supra* note 23, at 240 (“[T]he very purpose of the Federal Food, Drug, and Cosmetic Act (FDCA) [is] to protect the public by ensuring that pharmaceutical drugs are safe and effective for their intended uses.”); Greenwood, *supra* note 19, at 292 (“A study of 106 statements about drugs made by pharmaceutical sales representatives over the course of thirteen lunchtime presentations in 1993 found that eleven percent of the statements were inaccurate, and that physicians generally failed to recognize the inaccuracies.”).

232. 21 U.S.C. § 393(b)(1).

233. *See id.* § 393(b)(1)-(2).

false or misleading, pharmaceutical representatives' motivation to sell more drugs likely biases their off-label commercial speech.²³⁴ Pharmaceutical representatives' off-label use pitches encourage physicians to prescribe drugs for unapproved uses, irrespective of whether the information conveyed is complete or based on conclusive studies.²³⁵ The *Caronia* court should have concluded that off-label pharmaceutical marketing is more likely to deceive than to inform²³⁶ and that the First Amendment therefore does not protect off-label pharmaceutical marketing.²³⁷

The court's second conclusion, that the First Amendment protected the speech because it concerned lawful off-label drug use was a questionable decision.²³⁸ Under *Central Hudson*, commercial speech "must concern lawful activity" to merit First Amendment protection.²³⁹ While off-label prescribing is undoubtedly legal,²⁴⁰ the

234. See Dresser & Frader, *supra* note 27, at 478, for a brief overview of how market forces drive pharmaceutical manufacturers' decisions. See *id.* at 476, for an explanation of the competing interests involved in off-label prescribing and the effects of those interests on availability and accuracy of information. Dresser & Frader state, "In the current situation, the medical community has primary responsibility for determining when off-label prescribing is appropriate for patients. But appropriate off-label prescribing can be challenging for physicians today, because of time pressures, information overload, and the involvement of [the pharmaceutical] industry in research and education about off-label uses." *Id.*

235. See, for example, *Amarin Pharma, Inc. v. United States Food and Drug Administration*, 119 F. Supp. 3d 196, 210 (S.D.N.Y. 2015), in which Amarin Pharma, Inc. wanted to market its drug Vascepa for off-label use in patients with persistently high triglyceride levels as a treatment to "prevent major cardiovascular events in high-risk patients." In that case, "the FDA refused to approve Amarin's proposed new use for Vascepa," because "the 'clinical rationale,' or premise, of the . . . study had been that reducing triglyceride levels in that population would reduce the risk of cardiovascular events[,] [b]ut the results of the clinical trials involving other drugs that had also reduced triglyceride levels had yielded 'insufficient data to support a drug-induced change in serum [triglycerides] as a surrogate for reducing [cardiovascular] risk in [that] population.'" *Id.* at 212. The results of the clinical trial did not conclusively determine whether the off-label use reduced the risk of cardiovascular disease. *Id.*

236. See *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 563 (1980).

237. Cf. *United States v. Caronia*, 703 F.3d 149, 165 (2d Cir. 2012). Instead, the *Caronia* court took a different approach and concluded that "the promotion of off-label drug use is not in and of itself false or misleading." *Id.*

238. *Id.*

239. *Cent. Hudson*, 447 U.S. at 566.

240. *Good Reprint Practices*, *supra* note 84 ("[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.").

acts of introducing misbranded drugs into interstate commerce and causing the introduction of misbranded drugs into interstate commerce are both prohibited.²⁴¹ Arguably, a pharmaceutical sales representative who markets a drug off-label is engaging in speech that concerns his own illegal activity, that is, *promoting* or *causing* the interstate sale of a misbranded drug under the FDCA.²⁴² If the *Caronia* court had found that the speech related to unlawful activity, then it would have ended its analysis and upheld the FDA's prohibition.²⁴³

2. *The Caronia Court's Correct Application of the Second Central Hudson Factor*

The *Caronia* court did not end its inquiry at the first factor of the *Central Hudson* test because it found that the First Amendment protected off-label marketing.²⁴⁴ The court continued its analysis at the second step of the inquiry: whether the asserted government interest is substantial.²⁴⁵ The court concluded that "the government's asserted interests in drug safety and public health are substantial. Specifically, the government asserts an interest in preserving the effectiveness and integrity of the FDCA's drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs."²⁴⁶ The court correctly applied this step of the inquiry and moved on to the next factor.²⁴⁷

3. *The Caronia Court's Incorrect Application of the Third Central Hudson Factor*

The third *Central Hudson* factor is "whether the regulation directly advances the governmental interest asserted."²⁴⁸ The *Caronia* court held that the FDA's prohibition against off-label marketing does not directly advance the FDA's asserted interests for several reasons.²⁴⁹ First, it found that since doctors are not regulated by the

241. 21 U.S.C. § 331(a) (2012).

242. *See id.*

243. *See Cent. Hudson*, 447 U.S. at 566. *Cf. Caronia*, 703 F.3d at 165-66.

244. *Caronia*, 703 F.3d at 165-66.

245. *See Cent. Hudson*, 447 U.S. at 564-66; *Caronia*, 703 F.3d at 165-66.

246. *Caronia*, 703 F.3d at 166.

247. *See id.*

248. *Cent. Hudson*, 447 U.S. at 566.

249. *Caronia*, 703 F.3d at 166-67.

FDA and may prescribe drugs for off-label uses,²⁵⁰ the FDA's prohibition on off-label marketing by pharmaceutical companies does not reduce patient exposure to unsafe and ineffective drugs because it cannot prevent patients from taking drugs that physicians prescribe for off-label uses.²⁵¹ The court also cited its own finding that off-label promotion is not inherently false or misleading, and in particular that *Caronia's* speech was not false or misleading, to support the further conclusion that the FDA's prohibition against off-label marketing actually harmed patients who would benefit from investigational, off-label drugs if their doctors could receive truthful, non-misleading information about the drugs from sales representatives.²⁵² The court reasoned that since prescribing and using drugs off-label is lawful, the FDA's decision to restrict the flow of information about off-label uses by prohibiting off-label marketing did not advance the government's interest in protecting consumers.²⁵³

The *Caronia* court's opinion and conclusions are poorly reasoned as to this factor because its premises are flawed. As a preliminary matter, it is important to note that even though the FDA does not regulate physicians, and even though physicians may prescribe drugs for off-label uses, physicians have a duty to use their best medical judgment when treating patients and to conform treatment at least to the applicable medical standard of care.²⁵⁴ A

250. See *supra* text accompanying notes 81-84.

251. *Caronia*, 703 F.3d at 166.

252. *Id.* at 166-67.

253. *Id.* at 167 ("The government's construction of the FDCA essentially legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome. If the government's objective is to shepherd physicians to prescribe drugs only on-label, criminalizing manufacturer promotion of off-label use while permitting others to promote such use to physicians is an indirect and questionably effective means to achieve that goal. Thus, the government's construction of the FDCA's misbranding provisions does not directly advance its interest in reducing patient exposure to off-label drugs or in preserving the efficacy of the FDA drug approval process because the off-label use of such drugs continues to be generally lawful.")

254. See *Dresser & Frader*, *supra* note 27, at 476 ("Off-label prescribing is an integral part of contemporary medicine. Many patients benefit when they receive drugs or devices under circumstances not specified on the label approved by the Food and Drug Administration (FDA). An off-label use may provide the best available intervention for a patient, as well as the standard of care for a particular health problem."); *Good Reprint Practices*, *supra* note 84 ("[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific

physician may be liable for malpractice if his care for a patient does not meet the applicable medical standard of care whether he prescribed an off-label drug or not.²⁵⁵ While the FDA does not regulate off-label prescribing, the same standards of care that regulate other medical practices apply to off-label prescribing and negative consequences exist for physicians who negligently harm patients with off-label drugs.²⁵⁶ The *Caronia* court should not have intimated that physicians prescribe drugs off-label without any legal restrictions and without giving any thought to possible harmful effects to patients.²⁵⁷ Physicians must be fully informed about how and why off-label drugs are prescribed in their medical fields²⁵⁸ and thus the *Caronia* court should not have attributed any detriment to patients harmed by physicians' off-label prescribing as a failure of the FDA's regulatory system.²⁵⁹ The point the court failed to grasp is that there is risk inherent in off-label prescribing and that without accurate, reliable information about off-label uses, patients might be harmed by an off-label prescription.²⁶⁰

With an inaccurate view of off-label prescribing in mind, the *Caronia* court asserted that off-label promotion is not inherently false or misleading, which, although true, is not the correct inquiry

reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.”).

255. See Dresser & Frader, *supra* note 27, at 476 (“Of course, like other parts of medical practice, off-label prescribing can lead to malpractice liability if it fails to conform to accepted standards of care.”).

256. See *id.*

257. *Caronia*, 703 F.3d at 167 (“[T]he off-label use of such drugs continues to be generally lawful.”).

258. “Off-Label” and Investigational Use, *supra* note 82 (“Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.”).

259. *Caronia*, 703 F.3d at 167.

260. According to Dresser and Frader,

When scientific and medical evidence justify off-label uses, physicians promote patients’ interests by prescribing products off label. Off-label prescribing can also harm patients, however. The potential for harm is greatest when an off-label use lacks a solid evidentiary basis. A 2006 study examining prescribing practices for 169 commonly prescribed drugs found high rates of off-label use with little or no scientific support.

Dresser & Frader, *supra* note 27, at 476.

under *Central Hudson*.²⁶¹ Rather, the court should have concluded that off-label promotion by pharmaceutical sales representatives is more likely to mislead than to inform because insufficient information exists regarding the safety and effectiveness of off-label uses before those uses have been proven in clinical trials.²⁶² From that conclusion, used as a new premise, the court would then have correctly determined that off-label promotion that is more likely to mislead than to inform is also more likely to harm patients than benefit them, especially when the patients' physicians relied on incomplete promotional material when prescribing the drugs.²⁶³ The *Caronia* court should have concluded that the FDA's ban on off-label promotion directly advances the government's substantial interest in ensuring the safety and effectiveness of drugs because it minimizes the risks to patients involved in off-label prescribing.²⁶⁴

4. *The Caronia Court's Incorrect Application of the Fourth Central Hudson Factor*

The *Caronia* court moved on to the fourth prong of the *Central Hudson* analysis,²⁶⁵ which examines whether the government's regulation is only as extensive as necessary to achieve the asserted government interest.²⁶⁶ The court concluded that the FDA's ban was more extensive than necessary to further the government's interests in protecting public health and ensuring the safety and efficacy of

261. See *supra* Subsection IV.A.1.

262. See *supra* Subsection IV.A.1.

263. See Waxman, *supra* note 36, at 299 ("The FDCA's restrictions on misleading and unsubstantiated promotional claims are central to its goal of preventing injury from dangerous and deceptive products. . . . As shown in a wealth of congressional documents, the history of the FDCA demonstrates beyond question that without premarket safety and effectiveness requirements, deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives."); Dresser & Frader, *supra* note 27, at 476 ("When substantial uncertainty exists about off-label applications, patients are at risk of receiving harmful or ineffective treatments.").

264. Cf. *Caronia*, 703 F.3d at 166 ("[P]rohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.").

265. See *id.* at 167.

266. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 566 (1980).

drugs because feasible, less stringent alternatives to the FDA's criminal ban on off-label promotion existed to achieve the same objectives.²⁶⁷ However, though the *Central Hudson* Court used the phrase "not more extensive than is necessary" to define the parameters of the fourth prong,²⁶⁸ the Supreme Court later refined its inquiry in a way that gives more deference to the regulatory choices made by the government with respect to restrictions on commercial speech.²⁶⁹ The Court explained that the phrase "not more extensive

267. See *Caronia*, 703 F.3d at 167-68 ("[T]he government's construction of the FDCA to impose a complete and criminal ban on off-label promotion by pharmaceutical manufacturers is more extensive than necessary to achieve the government's substantial interests. Numerous, less speech-restrictive alternatives are available, as are non-criminal penalties.").

268. *Cent. Hudson*, 447 U.S. at 566 ("[W]e must determine whether the regulation . . . is not more extensive than is necessary to serve [the government's] interest.").

269. In *Board of Trustees of the State University of New York v. Fox*, Justice Scalia explained the rationale for not requiring the government to use the least restrictive means under the *Central Hudson* analysis:

Our cases have repeatedly stated that government restrictions upon commercial speech may be no more broad or no more expansive than "necessary" to serve its substantial interests. If the word "necessary" is interpreted strictly, these statements would translate into the "least-restrictive-means" test. . . . There are undoubtedly formulations in some of our cases that support this view—for example, the statement in *Central Hudson* itself that "if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive." We have indeed assumed in dicta the validity of the "least-restrictive-means" approach. However . . . the word "necessary" is sometimes used more loosely. And other formulations in our commercial speech cases support a more flexible meaning for the *Central Hudson* test. . . . Whatever the conflicting tenor of our prior dicta may be, we now focus upon this specific issue for the first time, and conclude that the reason of the matter requires something short of a least-restrictive-means standard.

Our jurisprudence has emphasized that "commercial speech [enjoys] a limited measure of protection, commensurate with its subordinate position in the scale of First Amendment values," and is subject to "modes of regulation that might be impermissible in the realm of noncommercial expression." The ample scope of regulatory authority suggested by such statements would be illusory if it were subject to a least-restrictive-means requirement, which imposes a heavy burden on the State.

We have refrained from imposing a least-restrictive-means requirement—even where core political speech is at issue—in assessing the validity of so-called time, place, and manner restrictions. We uphold such restrictions so long as they are "narrowly tailored" to serve a significant governmental interest, a standard that we have not interpreted

than is necessary” did not mean that the regulation must use the least restrictive means available or eliminate alternatives.²⁷⁰ Rather, the government’s regulation must employ means that are reasonable, proportionate, and narrowly tailored to achieve the end.²⁷¹ “Within those bounds,” stated the Court, “we leave it to governmental decisionmakers to judge what manner of regulation may best be employed.”²⁷² The government has some leeway to choose the most effective regulation from among various alternatives and need not choose the least restrictive alternative.²⁷³

If the *Caronia* court had used this revised standard under the fourth prong of the *Central Hudson* test, then the fact that there were feasible, less-restrictive alternatives to the FDA’s off-label promotion ban would not have caused it to conclude that the regulation failed under the fourth factor.²⁷⁴ Under *Central Hudson*, as later clarified by the Supreme Court, the government is permitted to restrict commercial speech to achieve a substantial government interest by any *reasonable* means that are narrowly tailored to the goal.²⁷⁵ The *Caronia* court should have granted the FDA the deference it is allowed under *Central Hudson* and *Fox*.²⁷⁶

to require elimination of all less restrictive alternatives In requiring that to be “narrowly tailored” to serve an important or substantial state interest, we have not insisted that there be no conceivable alternative, but only that the regulation not “burden substantially more speech than is necessary to further the government’s legitimate interests.” And we have been loath to second-guess the Government’s judgment to that effect. While these two lines of authority do not of course govern here, we think it would be incompatible with the asserted “subordinate position [of commercial speech] in the scale of First Amendment values” to apply a more rigid standard in the present context.

492 U.S. 469, 476-78 (1989) (citations omitted).

270. See *id.*; *Cent. Hudson*, 447 U.S. at 566.

271. *Fox*, 492 U.S. at 480 (“In sum . . . we have not gone so far as to impose upon [regulators] the burden of demonstrating that . . . the manner of restriction is absolutely the least severe that will achieve the desired end. What our decisions require is a “fit” between the legislature’s ends and the means chosen to accomplish those ends,—a fit that is not necessarily perfect, but reasonable; that represents not necessarily the single best disposition but one whose scope is ‘in proportion to the interest served,’; that employs not necessarily the least restrictive means but, as we have put it in the other contexts discussed above, a means narrowly tailored to achieve the desired objective.”).

272. *Id.*

273. *Id.*

274. See *United States v. Caronia*, 703 F.3d 149, 167-68 (2d Cir. 2012).

275. See *Fox*, 492 U.S. at 476-80.

276. *Id.*

From a deferential standpoint, the FDA's ban on off-label promotion by pharmaceutical companies is not unreasonable. The FDA's substantial government interests are to promote and protect public health by ensuring that drugs are safe and effective for their intended uses²⁷⁷ and to preserve the integrity of the FDA's new drug approval process through which the FDA furthers its goals for public health.²⁷⁸ The FDCA also requires the FDA to ensure that the marketing efforts of drug manufacturers do not produce promotional materials that are false or misleading.²⁷⁹ Although off-label promotional speech is not inherently false or misleading, the truthful or non-misleading nature of the speech cannot be demonstrated until rigorous clinical testing has conclusively proven the safety and effectiveness of an off-label use.²⁸⁰ In the past, false and misleading promotional speech from pharmaceutical companies caused harm to people who relied on representations that the drugs would perform as stated for the drugs' advertised uses.²⁸¹ The FDA thus promulgated the prohibition on off-label promotion as one rational way to prevent false or misleading promotional speech from causing harm to patients.²⁸²

5. *The FDA's Regulation Passes the Test for Restrictions on Commercial Speech*

Under *Central Hudson*, the FDA's prohibition against off-label marketing passes the test as a restriction on commercial speech that

277. 21 U.S.C. § 393(b)(1)-(2) (2012); see also *Caronia*, 703 F.3d at 166 (“[T]he government’s asserted interests in drug safety and public health are substantial. Specifically, the government asserts an interest in preserving the effectiveness and integrity of the FDCA’s drug approval process, and an interest in reducing patient exposure to unsafe and ineffective drugs.”).

278. See *Klasmeier & Redish*, *supra* note 15, at 315-16 (“While [FDA-approved drugs] have been vetted and approved by the FDA for their designated purpose, at no point has the FDA reviewed the supporting scientific data to determine efficacy for the off-label purpose. . . . [W]idespread off-label use of prescription drugs and devices conceivably undermines the FDA’s authority and deters manufacturers from seeking on-label FDA approval for even widespread alternative uses.”).

279. 21 U.S.C. § 393(b)(1)-(2) (2012).

280. *Id.* § 355(b)(1)(A) (requiring all new drug applications to include “full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use” before approval).

281. See *supra* Part I-Section I.A.

282. See *supra* Section I.B.

does not violate the First Amendment.²⁸³ Contrary to the conclusion of the *Caronia* court, off-label promotion is more likely to mislead than to inform.²⁸⁴ The regulation also directly advances the substantial government interest in ensuring the safety and efficacy of drugs.²⁸⁵ Additionally, the regulation is narrowly tailored and reasonably related to achieving the government's goals.²⁸⁶ Although the FDA's method of ensuring public safety and welfare by prohibiting off-label promotion is constitutional, that method is also practically problematic because it hinders information about off-label uses from circulating freely.²⁸⁷

B. Practical Problems, Policy Arguments, and a Proposed Solution

Despite the prohibition's decided constitutionality, the ban problematically covers truthful, non-misleading promotional speech in addition to the false and misleading promotional speech that it rightly quashes.²⁸⁸ This practical problem prevents some valuable information about off-label indications from passing from the pharmaceutical companies that possess it to the physicians who would put it to good use.²⁸⁹ Many opponents of the FDA's ban on

283. See *supra* Subsections IV.A.1-4.

284. See *supra* Subsection IV.A.1.

285. See *supra* Subsection IV.A.3.

286. See *supra* Subsection IV.A.4.

287. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 213 (S.D.N.Y. 2015) (“Such doctors . . . ‘need truthful and non-misleading information about these drugs to make informed decisions about what is best for their patients,’ but the ‘[FDA]’s current regime for regulating the flow of “off-label” information to doctors about prescription drugs . . . severely restricts medical professionals’ access to information from the source most knowledgeable about the drugs: the drug manufacturers” (quoting Pl.’s Compl., *supra* note 97, ¶ 3)).

288. See *Osborn*, *supra* note 25, at 305-06 (“[I]nvariably there will be occasions in which the [pharmaceutical] company is in possession of truthful, non-misleading scientific and medical information [about off-label uses] that will not be included in the current, approved labeling.”); *Greenwood*, *supra* note 19, at 297-98 (“[T]here is no way to gain the benefits of false advertising law without sweeping in some truthful speech. . . . Given medicine’s high stakes, it is neither surprising nor unconstitutional that the prophylactic rule that governs drug claims suppresses some truthful speech.”).

289. See *Osborn*, *supra* note 25, at 306 (explaining that the ban on off-label promotion “limits the full dissemination to prescribing physicians of useful medical information”); “*Off-Label*” and *Investigational Use*, *supra* note 82 (“Good medical practice and the best interests of the patient require that physicians use legally available drugs . . . according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the

off-label promotion argue that, from a public policy perspective, the ban causes serious harm to the pharmaceutical industry and to patients who would benefit from more widespread information regarding investigational, off-label drugs.²⁹⁰

As enacted in 1938 and amended in 1962, the purpose of the FDCA was to reduce the risk of harm to patients posed by unsafe and ineffective drugs.²⁹¹ The FDCA addressed the problem through a twofold solution: (1) the statute required informative labeling to ensure that customers received accurate information about the drugs they purchased or used²⁹² and (2) the statute made it a crime to misbrand a drug, either by mislabeling or otherwise misrepresenting facts about the drug.²⁹³ Both of these statutory innovations concerned the amount and quality of information disseminated about drugs.²⁹⁴ The provisions on labeling seek to provide the public with more

responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.”).

290. See Osborn, *supra* note 25, at 301, 303 (“[T]he single greatest threat to the pharmaceutical industry may be the policy environment within the United States, which is restricting the ability of companies to speak truthfully with physicians about their products.”); Klasmeier & Redish, *supra* note 15, at 316 (“[W]hile it is true that the ban on off-label promotion by manufacturers prevents false or misleading advertising, because the ban is all-inclusive it simultaneously prevents promotion of valuable off-label uses of which doctors may well be unaware. . . . As a result, in many instances doctors are likely to be deprived of valuable information about important off-label uses that are totally lawful and extremely beneficial to some very sick people.”).

291. See *supra* Part I-Section I.A.

292. 21 U.S.C. § 352(a)-(c), (e)(1)(A)(i)-(iii) (2012) (“A drug or device shall be deemed to be misbranded—(a) [i]f its labeling is false or misleading in any particular . . . (b) [i]f in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count . . . (c) [i]f any word, statement, or other information required by or under authority of this chapter to appear on the label or labeling is not prominently placed thereon with such conspicuousness . . . and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use . . . (e)(1)(A) [i]f it is a drug, unless its label bears, to the exclusion of any other nonproprietary name . . . (i) the established name . . . of the drug, if there is such a name; (ii) the established name and quantity or, if determined to be appropriate by the Secretary, the proportion of each active ingredient . . . and (iii) the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary, on the immediate container . . .”).

293. *Id.* § 331.

294. *Id.* §§ 331, 352(a)-(c), (e)(1)(A)(i)-(iii).

accurate information about the drugs.²⁹⁵ The provisions prohibiting misbranding seek to protect the public by reducing the amount of false and misleading information in circulation.²⁹⁶ The statute as a whole seeks to regulate the information available by promoting or requiring factual, accurate information, while prohibiting false or inaccurate information.²⁹⁷ While no difficulty exists in applying these provisions when those in the pharmaceutical and medical industries know what information is false and what information is true, a problem arises when little or nothing is known about the safety and efficacy of a drug's uses.²⁹⁸

In the context of off-label drug use, the inherent problem is the lack of tested and proven information about the safety and effects of the drugs.²⁹⁹ For an off-label use, both the degree of risk of harm from the drug and the accuracy of statements made about the drug are unknown.³⁰⁰ Yet both sides of the policy argument surrounding off-label promotion agree that doctors need reliable information to

295. *Id.* § 352(a)-(c), (e)(1)(A)(i)-(iii).

296. *Id.* § 331.

297. *Id.* §§ 331, 352(a)-(c), (e)(1)(A)(i)-(iii).

298. *See* Dresser & Frader, *supra* note 27, at 476 (“When substantial uncertainty exists about off-label applications, patients are at risk of receiving harmful or ineffective treatments. . . . In a perfect world, all uses of drugs and devices would be supported by solid research. The existing regulatory system fails to impose this high standard, however, and the private sector often lacks incentives to conduct rigorous evaluations of off-label uses.”).

299. Dresser and Frader explain the valuable information generated through clinical trials and the FDA’s new drug approval process:

FDA officials evaluate safety and effectiveness [for each new drug] and determine whether the probability and magnitude of potential benefits are sufficient to justify a product’s risks. . . . [T]he FDA review process . . . generally produces high-quality information that enhances clinical practice. In most cases, the FDA review process gives physicians a reasonable evidentiary basis for on-label prescribing. But the initial FDA review fails to answer whether a product should be used off label. A product may be safe and effective for one indication, but could present a different risk-benefit ratio for another indication. . . . When FDA officials approve a product, they approve a specific label for that product, too. The label includes information about the approved indications for product use, as well as the approved dosage, method of administration, and patient population.

Dresser & Frader, *supra* note 27, at 477 (internal footnotes omitted). Because the FDA does not review all possible uses of a drug for safety and efficacy, and because the manufacturers do not run clinical trials for all possible uses, often no reliable information about those uses is available to physicians. *Id.*

300. *Id.*

make proper care recommendations to their patients.³⁰¹ As a practical solution to this policy problem, the FDA should balance the risks caused by scientific uncertainty by allowing manufacturers to circulate some information about off-label uses to physicians, but it should restrict the authorized information to the factual results and logical inferences obtained from clinical trials, even if the clinical trials are not conclusive as to the safety and effectiveness of the off-label use.³⁰² If physicians were able to see unbiased results of clinical trials, even if the results were inconclusive, they would at least have some reliable scientific information about the possible uses, doses, side effects, and initial results than if they did not have that access.³⁰³ The FDA should allow pharmaceutical companies to step into this information-dissemination role once they have completed clinical trials and submitted a supplemental new drug application to the FDA for a particular off-label use in order to preserve the integrity of the drug approval process.³⁰⁴ As the *Caronia* court reasonably stated, off-label promotional speech is not inherently false or misleading,³⁰⁵ and accordingly the FDA should propose a rulemaking by which it would allow pharmaceutical companies to draft factual, truthful, unbiased, and non-misleading statements about the results of the companies' most recent clinical trials to disseminate to physicians who desire reliable information about an off-label use.³⁰⁶

301. Compare Osborn, *supra* note 25, at 306, and Klasmeier & Redish, *supra* note 15, at 316 (both citing physicians' need for information about off-label drugs as one reason to repeal the FDA's prohibition on off-label marketing), with 21 U.S.C. §§ 331, 352(a)-(c), (e)(1)(A)(i)-(iii) (requiring more, accurate information on drug labels for the purpose of protecting patients).

302. See *supra* note 299.

303. Cf. *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 213 (S.D.N.Y. 2015) ("Such doctors . . . 'need truthful and non-misleading information about these drugs to make informed decisions about what is best for their patients,' but the '[FDA]'s current regime for regulating the flow of "off-label" information to doctors about prescription drugs . . . severely restricts medical professionals' access to information from the source most knowledgeable about the drugs: the drug manufacturers . . .'" (quoting Pl.'s Compl., *supra* note 97, ¶ 3)).

304. See also Klasmeier & Redish, *supra* note 15, at 316 ("[W]idespread off-label use of prescription drugs and devices conceivably undermines the FDA's authority and deters manufacturers from seeking on-label FDA approval for even widespread alternative uses."). As reported in *Amarin Pharma, Inc.*, 119 F. Supp. 3d at 214-15, Amarin requested that the FDA allow it to circulate promotional statements, preapproved by the FDA, based on its latest clinical trials of an off-label use of one of its drugs.

305. *Caronia*, 703 F.3d at 165.

306. Cf. *supra* text accompanying notes 101-03.

In *Amarin Pharma, Inc. v. U.S. Food and Drug Administration*, the pharmaceutical manufacturer Amarin wanted to disclose to physicians the results of clinical trials of its drug Vascepa, which had been proven to lower high triglyceride levels, but which had unclear implications for prevention of cardiovascular disease.³⁰⁷ Amarin wanted to use plain, straightforward statements of fact about the results of the testing, including the extent to which the off-label use had been proven effective and the extent to which the tests had been inconclusive.³⁰⁸ The trial court ultimately agreed that the information Amarin wanted to use as promotional materials was truthful and non-misleading, and following the *Caronia* court, found that to decide otherwise would pose a First Amendment issue.³⁰⁹ While, contrary to the *Caronia* and *Amarin* courts' view, the First Amendment does not conflict with the FDA's off-label marketing prohibition,³¹⁰ the FDA should appreciate the practical value and benefit that would come from allowing pharmaceutical manufacturers to use factual, non-misleading information about the results of clinical trials as promotional materials for off-label uses.³¹¹

The FDA might resist such a policy on two grounds: (1) allowing pharmaceutical manufacturers to market drugs off-label will undermine the integrity of the drug approval process because the manufacturers would not have an incentive to file a supplemental new drug application for the off-label use³¹² and (2) it is not possible to have any accurate information before clinical trials have conclusively shown that an off-label use either is or is not safe and effective.³¹³ First, this solution will not undermine the drug approval process because pharmaceutical manufacturers would be required to submit a supplemental new drug application before assuming the information-dissemination role.³¹⁴ Second, this solution does not

307. *Amarin Pharma, Inc.*, 119 F. Supp. 3d at 212-15.

308. *Id.*

309. *Id.* at 237.

310. *See supra* Section IV.A.

311. *Cf. Klasmeier & Redish, supra* note 15, at 316 (“[W]hile it is true that the ban on off-label promotion by manufacturers prevents false or misleading advertising, because the ban is all-inclusive it simultaneously prevents promotion of valuable off-label uses of which doctors may well be unaware. . . . As a result, in many instances doctors are likely to be deprived of valuable information about important off-label uses that are totally lawful and extremely beneficial to some very sick people.”).

312. *See supra* text accompanying note 91.

313. GUIDANCE FOR INDUSTRY, *supra* note 28, at 2-3.

314. *See supra* text accompanying note 304.

claim to eliminate all risk from off-label marketing and prescribing, but balances the risk inherent in off-label use with the public's need for information.³¹⁵ Patients benefit from off-label uses when physicians, in their best medical judgment, properly prescribe those uses, and it is the FDA's responsibility to facilitate dissemination of the most reliable and up-to-date information available.³¹⁶

Pharmaceutical manufacturers also might object that the FDA should allow them to market off-label without any restrictions or requirement that they file supplemental new drug applications before doing so, as the *Caronia* and *Amarin* courts were inclined to allow.³¹⁷ However, the health and safety of patient-consumers remains the goal of the FDCA, and the means chosen by the FDA to regulate the pharmaceutical industry must reflect that goal.³¹⁸ Also, under *Central Hudson*, any regulation of commercial speech must be narrowly tailored to achieve the government's substantial interest.³¹⁹ The FDA must uphold the regulatory process, and so the FDA must incentivize manufacturers to file new drug approvals for off-label uses.³²⁰

In summary, although the *Caronia* court found the FDA's ban on off-label promotion to be an unconstitutional violation of the First Amendment, the court misapplied the *Central Hudson* test for restrictions on commercial speech and should have upheld the prohibition.³²¹ While the ban is constitutional, the FDA's policy is practically problematic because it restricts the flow of information about off-label uses and prevents physicians from receiving scientifically verified information when the FDA has not yet approved an off-label use.³²² Therefore, the FDA should adopt a policy allowing pharmaceutical manufacturers to present factual

315. See *supra* text accompanying notes 299-302.

316. See Dresser & Frader, *supra* note 27, at 476.

317. United States v. Caronia, 703 F.3d 149, 168-69 (2d Cir. 2012); *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 237 (S.D.N.Y. 2015).

318. See Waxman, *supra* note 36, at 299 ("The FDCA's restrictions on misleading and unsubstantiated promotional claims are central to its goal of preventing injury from dangerous and deceptive products. . . . As shown in a wealth of congressional documents, the history of the FDCA demonstrates beyond question that without premarket safety and effectiveness requirements, deceptive, unsubstantiated claims about health-related products proliferate, at a tremendous cost in human lives.").

319. Bd. of Trs. of State Univ. of N.Y. v. Fox, 492 U.S. 469, 480 (1989).

320. See Klasmeier & Redish, *supra* note 15, at 316.

321. See *supra* Section IV.A.

322. See *supra* Section IV.B.

statements about the results of clinical trials for an off-label use to physicians, after the manufacturer files a supplemental new drug application for that use, even if the studies are inconclusive.³²³

CONCLUSION

Although the Second Circuit found that the FDA's regulatory ban on off-label pharmaceutical marketing violates the First Amendment,³²⁴ the marketing policy is constitutional and the First Amendment does not stand in the way.³²⁵ In *United States v. Caronia*, the Second Circuit misapplied the *Central Hudson* test for whether a government regulation constitutionally restricts commercial speech, an error that should be recognized on review by the Supreme Court in an appropriate case.³²⁶ Despite the constitutionality of the FDA's chosen regulation, there is a need for dissemination of truthful, non-misleading information regarding off-label uses.³²⁷ The FDA should allow pharmaceutical companies and their representatives to fill that need by providing factual, informative, and unbiased summaries of the most up-to-date medical research for unapproved uses of drugs to prescribing physicians.³²⁸

323. See *supra* Section IV.B.

324. See *supra* Section III.A.

325. See *supra* Section IV.A.

326. See *supra* Section IV.A.

327. See *supra* Section IV.B.

328. See *supra* Section IV.B.