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Erratum

UNITED STATES V. CARONIA: OFF-LABEL DRUG PROMOTION AND FIRST AMENDMENT BALANCING

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Off-label drug promotion is commonplace in the United States, but it is not without its dangers. While the Food, Drug, and Cosmetic Act does not explicitly ban off-label promotion, the Food & Drug Administration (FDA)—in order to protect consumers from unsafe and ineffective drugs—has taken steps to regulate it. The FDA does so through its intended-use regulation, which lists the types of evidence the FDA can consider in determining whether a drug is misbranded. It is a crime to sell a misbranded drug into interstate commerce or to conspire to do so. On September 25, 2015, the FDA proposed an amendment to the regulation, which has drawn opposition from various industry groups due to its potential to restrict the type of speech that is often used in off-label promotion.

The First Amendment challenge to the proposed amendment rests on United States v. Caronia*, in which the FDA was prevented from using truthful, nonmisleading speech to convict a pharmaceutical representative of a conspiracy to sell a misbranded drug. This Note examines whether the amendment to the regulation is permissible under* Caronia*. It first contends that the regulation does not facially violate the First Amendment. It further argues that the rule is constitutional and does not pose the same First Amendment issue as was seen in* Caronia *as long as the FDA implements it with care. This Note concludes by exploring various ways that the FDA can constitutionally regulate off-label drug promotion under the proposed rule.*

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INTRODUCTION

On January 15, 2009, the pharmaceutical giant Eli Lilly and Company agreed to pay a $515 million fine.[1] At the time, it was the largest criminal fine ever imposed on a U.S. corporation.[2] This record stood for less than eight months—on September 2, 2009, Pfizer, another drug manufacturer,

1. *Eli Lilly Fined Nearly $1.5B in Drug Marketing Case*, CNN (Jan. 15, 2009, 3:26 PM), http://money.cnn.com/2009/01/15/news/companies/eli_lilly/ [https://perma.cc/RS9P-DGZY].

2. *Id.*

agreed to pay $1.3 billion in restitution to settle criminal charges.[3] These are just two of the recent massive settlements between the government and pharmaceutical companies.[4] Common to all the settlements is that they arose from the illegal promotion of drugs for unapproved, potentially dangerous uses.

Under the Food, Drug, and Cosmetic Act (FDCA), a drug manufacturer must prove that a drug is safe and effective for each of its intended uses before it can be marketed for those indications.[5] This is a high bar to meet—studies needed to prove safety and effectiveness are expensive and often take years to complete, and the time it takes to get approval for a new indication can eat into a drug's patent exclusivity period.[6] But, while drug manufacturers cannot sell drugs for off-label uses, physicians can legally prescribe drugs for these uses.[7] Given the high costs of gaining FDA approval for a new indication, drug manufacturers are incentivized to promote drugs to prescribers for off-label uses. By doing so, a drug company can increase sales through increased prescriptions without waiting for FDA approval for these uses.

Using drugs for unapproved reasons can be dangerous. For example, the drug ketoconazole should be used only for serious infections due to its side effects, which include high risks of liver damage, adrenal gland problems, and harmful interactions with other medications.[8] However, in practice, the drug is prescribed solely for the minor skin and nail fungal infections for which the FDA deems it too dangerous.[9]

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3. Gardiner Harris, *Pfizer Pays $2.3 Billion to Settle Marketing Case*, N.Y. TIMES (Sept. 2, 2009), http://www.nytimes.com/2009/09/03/business/03health.html [https://perma.cc/7CL6-HLDB]. Pfizer paid a further $1 billion in civil fines. *Id.*

4. *See, e.g.*, Katie Thomas & Michael S. Schmidt, *Glaxo Agrees to Pay $3 Billion in Fraud Settlement*, N.Y. TIMES (July 2, 2012), http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html [https://perma.cc/F9VN-PPV7] (discussing how GlaxoSmithKline agreed to pay a $1 billion criminal penalty for promoting drugs for off-label uses); Katie Thomas, *J.&J. to Pay $2.2 Billion in Risperdal Settlement*, N.Y. TIMES (Nov. 4, 2013), http://www.nytimes.com/2013/11/05/business/johnson-johnson-to-settle-risperdal-improper-marketing-case.html [https://perma.cc/FEK5-7PB4] (discussing how Johnson & Johnson agreed to pay a $485 million criminal penalty and a $1.72 billion civil penalty due to improper off-label promotion).

5. An indication "refers to the use of [a] drug for treating a particular disease." Omudhome Ogbru, *Indications for Drugs (Uses), Approved vs. Non-Approved*, MEDICINENET.COM, https://www.medicinenet.com/script/main/art.asp?articlekey=20732 [https://perma.cc/P8EG-4STE] (last visited Mar. 15, 2018). See *infra* Part II.A for a discussion of the FDA's regulatory scheme for drugs.

6. *See infra* notes 46–50 and accompanying text.

7. *See, e.g.*, *Understanding Unapproved Use of Approved Drugs "Off Label,"* FOOD & DRUG ADMIN., https://www.fda.gov/forpatients/other/offlabel/default.htm [https://perma.cc/46R2-SHU7] (last visited Mar. 15, 2018) ("From the FDA perspective, once the FDA approves a drug, healthcare providers generally may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient.").

8. Meghan Ross, *Despite Patient Death, Off-Label Oral Ketoconazole Prescribing Continues*, PHARMACY TIMES (May 24, 2016), http://www.pharmacytimes.com/product-news/despite-patient-death-off-label-oral-ketoconazole-prescribing-continues [https://perma.cc/F9J9-EL9J].

9. *Id.* The FDA previously approved the drug for these uses; it authorized a label change to remove these indications in 2013. *Id.*; *see also* Samantha Olson, *Gabapentin Side Effects:*

Historically, the FDA has had wide leeway to regulate drug manufacturers' sale of medications for unapproved uses.[10] However, a recent Second Circuit decision, *United States v. Caronia*,[11] has thrown the FDA's ability to do so into doubt.[12] This decision holds that First Amendment concerns prevent the FDA from criminalizing off-label drug promotion that consists of truthful and nonmisleading speech. While some secondary commentary treats *Caronia* as a landmark case that has nationwide applicability, it is currently the law only in the Second Circuit,[13] and even there has been narrowly interpreted.[14]

The FDA's proposed amendment to the regulation regarding how the agency determines a drug's intended uses[15] must be analyzed against the backdrop of *Caronia* and its progeny. The amendment introduces a new "totality of the evidence" standard to the regulation to find a drug's intended uses, which some manufacturers fear will be used to expand the circumstances under which the FDA can determine the drug's intended uses.[16] Broadly speaking, a drug must be approved for each intended use before it can legally be introduced into interstate commerce for those uses.[17] If a manufacturer sells a drug for an unapproved use, then the company can be subject to a misbranding charge—a criminal violation of the FDCA.[18]

Drug manufacturers oppose the amendment in part because they fear it will be used to criminalize truthful, nonmisleading commercial speech[19] that is often used in off-label promotion.[20] Criminalization of such speech violates

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The Dangers of Off-Label Prescriptions' Surprising Side Effects, MED. DAILY (Nov. 9, 2016, 6:18 PM), http://www.medicaldaily.com/gabapentin-side-effects-dangers-label-prescriptions-surprising-side-effects-403998 [https://perma.cc/8NDH-HEWZ] (discussing a study that found that 80 percent of off-label prescriptions are not backed by strong scientific evidence and that patients prescribed drugs for off-label uses are more than twice as likely to suffer adverse side effects as compared to people taking drugs for their FDA-approved uses); Laura Perry, *Alzheimer's Drug Prescribed "Off-Label" for Mild Cognitive Impairment Could Pose Risk for Some*, UCLA (Feb. 23, 2017), http://newsroom.ucla.edu/releases/alzheimers-drug-prescribed-off-label-for-mild-cognitive-impairment-could-be-dangerous-for-some [https://perma.cc/3GKJ-WYU7] (discussing how Donepezil, a drug commonly prescribed off label to slow the progression of Alzheimer's, can accelerate cognitive decline in people with a specific genetic variant).

10. *See infra* Part II.A.

11. 703 F.3d 149 (2d Cir. 2012).

12. *See infra* Part II.B.

13. William S. Comanor & Jack Needleman, *The Law, Economics, and Medicine of Off-Label Prescribing*, 91 WASH. L. REV. 119, 133 (2016) ("The *Caronia* decision is controlling precedent in only . . . the Second Circuit. In forty-seven states, the FDA retains the authority to prohibit the marketing and promotion of off-label indications.").

14. *See infra* Part II.C.

15. Meaning of "Intended Uses," 21 C.F.R. § 201.128 (2018).

16. *See infra* Part I.C. This Note uses the term "uses" to refer to FDA-approved uses but acknowledges that certain drugs may only be approved for one use.

17. *See infra* Part I.A.

18. *See infra* Part I.A.

19. See *infra* Part I.B for a discussion of commercial speech.

20. *See* Letter from Advanced Med. Tech. Ass'n to FDA on Proposed Amendments to the Intended Use Regulation 1–2 (July 18, 2017), https://www.regulations.gov/document?D=FDA-2015-N-2002-2004 [https://perma.cc/MYF9-PAGX] ("FDA's Final Rule is inconsistent with . . . the First Amendment protection that extends to [truthful and nonmisleading]

the First Amendment, as the Supreme Court has recognized: "Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."[21] However, other authorities hold that the FDA is constitutionally permitted to use truthful, nonmisleading speech as evidence of a misbranding crime[22] as long as the government does not criminalize this type of speech.[23] If the government cannot use this speech to prove a misbranding offense, then off-label drug promotion based on such speech can continue unabated. However, if the government can permissibly use this type of speech as evidence in a misbranding case, then the FDA would be free to use the amended regulation to regulate off-label drug promotion in the appropriate circumstances.

This Note examines whether the FDA's amended intended-use regulation is permissible under the First Amendment and how the FDA can implement it to comply with the relevant case law. Part I of this Note provides an overview of the FDA's drug regulatory scheme and how it relates to off-label drug promotion, and it also discusses the relevant First Amendment law. Part II explores the case law addressing what evidence the FDA may use to find a drug's intended use, the *Caronia* decision, and reactions to *Caronia*. Part III examines whether the proposed amendment to the regulation violates the First Amendment. This Note argues that industry objections to the regulatory change are overblown and that if the totality of the evidence standard is not used to criminalize truthful, nonmisleading speech, then the regulation comports with the First Amendment. It then considers different instances of off-label promotion and how the FDA can permissibly use the regulation in those situations to regulate the promotion.

I. AN OVERVIEW OF DRUG REGULATION AND ITS INTERACTION WITH THE FIRST AMENDMENT

A drug manufacturer's intended use for a drug is crucial to determining whether the drug is misbranded. If the FDA concludes that a manufacturer sold a drug for an unapproved use, then that manufacturer may be subject to

communications."); Letter from Pharm. Research & Mfrs. of Am. to FDA on Proposed Amendments to the Intended Use Regulation 3 (July 18, 2017), http://src.bna.com/q3Z [https://perma.cc/YY8F-KD4F] ("[T]he First Amendment permits FDA to restrict [truthful and nonmisleading] speech only as a last resort . . . . Applying *Sorrell* and *Caronia* [to the proposed amendment to the intended-use regulation], enforcement actions for misbranding based on manufacturers' truthful and non-misleading communications with healthcare professionals about unapproved uses trigger heightened judicial scrutiny, and fail that standard."); *see also infra* notes 74–75.

21. Sorrell v. IMS Health Inc., 564 U.S. 552, 557 (2011); *see also infra* Part II.B.

22. *See infra* notes 27–39 and accompanying text.

23. *See, e.g.*, Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004) ("[T]he First Amendment allows 'the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.'" (quoting Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993))); *see also* Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2193, 2209 (Jan. 9, 2017) (to be codified at 21 C.F.R. pts. 201, 801, 1100) ("[FDA] do[es] not agree with the assertion that the current case law allows FDA to consider speech as evidence of intended use only when it is false or misleading.").

a misbranding action. Therefore, the types of evidence that the FDA may consider in determining a drug's intended use for purposes of a misbranding action are essential to deciding when the government can prosecute a drug company for off-label promotion. First Amendment implications are particularly pressing: when the government uses speech utilized in off-label promotion in a misbranding action, courts must consider whether this abridges the freedom of speech.

Part I.A discusses the FDA's drug regulatory scheme and the importance of a drug's intended use. Part I.B then considers commercial speech and how government regulations of such speech are analyzed. Part I.C concludes by providing an overview of the amended intended-use regulation and industry concerns about its potential to illegally criminalize truthful, nonmisleading speech.[24]

A. The FDA's Drug Regulatory Scheme

Under the FDCA, drugs are, in part, "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals."[25] All drugs must be approved by the FDA for at least one indication before they can be introduced into interstate commerce.[26] A drug is misbranded when its labeling[27] lacks "adequate directions for use" for all uses.[28] "Adequate directions for use" are defined as "directions under which the layman can use a drug safely and for the purposes for which it is intended."[29] A drug's intended use is discerned through the FDA's intended-use regulation.[30]

While the FDA must approve each of a drug's intended uses before a manufacturer can sell it to physicians for those uses, health-care providers can prescribe drugs for unapproved uses.[31] Furthermore, the FDCA and its implementing regulations do not explicitly prohibit drug manufacturers or

24. Other industry concerns over the new rule include an alleged Administrative Procedure Act violation and Fifth Amendment Due Process issues. Letter from Paul E. Kalb et al. to Div. of Dockets Mgmt., FDA, Petition to Stay and for Reconsideration 10–13, 20–21 (Feb. 8, 2017), https://www.regulations.gov/contentStreamer?documentId=FDA-2016-N-1149-0048&attachmentNumber=1&contentType=pdf [https://perma.cc/8RPM-P9LV]. Such concerns are beyond the scope of this Note.

25. 21 U.S.C. § 321(g)(1)(B) (2012). The drug definition also includes "articles (other than food) intended to affect the structure or any function of the body of man or other animals." *Id.* § 321(g)(1)(C).

26. *See id.* § 355.

27. Labeling is defined as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." *Id.* U.S.C. § 321(m). Courts interpret the term "labeling" broadly. *See* Kordel v. United States, 335 U.S. 345, 350–52 (1948) (finding that manufacturer-printed pamphlets and circulars that are shipped separately from a product and that make claims about the efficacy of the product are labeling under the FDCA).

28. 21 U.S.C. § 352(f)(1).

29. Drugs; Adequate Directions for Use, 21 C.F.R. § 201.5 (2018).

30. See *infra* Part I.C for a discussion of this regulation.

31. *See supra* notes 5–7 and accompanying text.

their representatives from engaging in off-label promotion.[32] However, this has not stopped the government from prosecuting these actors for marketing drugs for unapproved uses.[33] The government finds authority to do so based on the adequate directions for use and intended-use regulations. When a manufacturer or its representative promotes a drug for an off-label use, the speech used in off-label promotion can give the drug a new intended use under the intended-use regulation.[34] Since an unapproved intended use cannot be present on a drug's labeling,[35] the labeling now does not have adequate directions for all intended uses, and that lack of adequate direction for use makes it misbranded.[36] Delivering a misbranded drug into interstate commerce is a crime,[37] as is conspiring to do so.[38] So, if a manufacturer or its representative sells a drug with an unapproved intended use or conspires to do so, then that actor commits a misbranding offense.[39]

Manufacturers can seek FDA approval for off-label uses. Before a drug can be sold, the FDA must approve its New Drug Application (NDA).[40] The application must show, in relevant part, that the drug is safe and effective for its intended uses and contain examples of the drug's labeling.[41] After the FDA approves an NDA, the NDA's owner "must notify FDA about each

32. Stephanie M. Greene, Debate, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. REV. ONLINE 239, 240 (2014) ("FDA regulations do not directly prohibit off-label promotion.").

33. United States. v. Caronia, 703 F.3d 149, 154 (2d Cir. 2012) ("The government has repeatedly prosecuted—and obtained convictions against—pharmaceutical companies and their representatives for misbranding based on their off-label promotion."). The court then listed examples of such prosecutions. *Id.*

34. *See* Greene, *supra* note 32, at 241 ("Oral statements by pharmaceutical representatives may be used as evidence of a manufacturer's intended use for a drug . . . ."); *infra* Part I.C (discussing the regulation).

35. *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 21 C.F.R. § 201.56(a)(3) (2018) ("No implied claims or suggestion of drug use may be made [on labeling] if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.").

36. Greene, *supra* note 32, at 241.

37. *See* 21 U.S.C. § 331(a) (2012) ("The introduction or delivery for introduction into interstate commerce of any . . . drug . . . that is . . . misbranded [is prohibited under the FDCA]."). Introducing a misbranded drug into interstate commerce is a criminal offense. *Id.* § 333(a)(1)–(2) ("Any person who violates a provision of section 331 of [title 21 of the U.S. Code] shall be imprisoned for not more than one year or fined not more than $1,000, or both . . . [I]f any person . . . commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.").

38. 18 U.S.C. § 371 (2012) ("If two or more persons conspire either to commit any offense against the United States, or to defraud the United States, or any agency thereof in any manner or for any purpose, and one or more of such persons do any act to effect the object of the conspiracy, each shall be fined . . . or imprisoned . . . ."); *see, e.g.*, United States v. Caronia, 703 F.3d 149, 152 (2d Cir. 2012) ("Caronia was found guilty of conspiracy to introduce a misbranded drug into interstate commerce, a misdemeanor violation of 21 U.S.C. §§ 331(a) and 333(a)(1).").

39. *See supra* notes 37–38.

40. 21 U.S.C. § 355(a)–(b); *see also New Drug Application (NDA)*, FDA (Mar. 29, 2016), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/newdrugapplicationnda/default.htm [https://perma.cc/3FU5-2M9Y].

41. 21 U.S.C. § 355(d).

change in each condition established in an approved NDA."[42] Changes in labeling that reflect a new indication require FDA approval before they can be implemented.[43]

Manufacturers are disincentivized from seeking approval for all of a drug's possible uses because the approval process is expensive and time consuming. For example, supplemental NDAs (sNDA), which the FDA must approve before a manufacturer can effectuate a labeling change, are extremely costly.[44] In 2017, a manufacturer must pay the FDA $1,019,050 for an approved sNDA.[45] More significantly, studies needed to prove that a drug is safe and effective typically cost millions of dollars.[46] Furthermore, the majority of such studies fail to prove that an off-label use is safe and effective, and successful studies typically take years to complete.[47] Waiting for completion of these studies and FDA approval of an sNDA can also cut into a drug's patent exclusivity period,[48] which further reduces the motivation to

42. Supplements and Other Changes to an Approved NDA, 21 C.F.R. § 314.70(a)(1)(i) (2018).

43. *Id.* § 314.70(b)(2)(v)(A).

44. *Id.* § 314.70(a)(1)(i) ("[T]he applicant must notify FDA about each change in each condition established in an approved NDA beyond the variations already provided for in the NDA."); FDA, GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA 24 (2004) (providing that "labeling changes associated with new indications and usage" must be approved by the FDA before they can be effectuated.).

45. Michael Mezher, *FDA Unveils User Fee Rates for FY 2017*, REG. AFF. PROFESSIONALS SOC'Y (Aug. 1, 2016), http://www.raps.org/Regulatory-Focus/News/2016/08/01/25478/FDA-Unveils-User-Fee-Rates-for-FY-2017/ [https://perma.cc/MCR3-6QUP]. An sNDA applicant receives a 75 percent refund if the application is ultimately rejected. 21 U.S.C. § 379h(a)(1)(D).

46. For example, by one estimate, a Phase 2 clinical trial costs, on average, $7 million to $19.6 million, and the cost of a Phase 3 trial ranges from $11.5 million to $52.9 million. Joe Martinez, *Driving Drug Innovation and Market Access: Part 1—Clinical Trial Cost Breakdown*, CTR. POINT CLINICAL SERVICES (Sept. 27, 2016), http://www.centerpointclinicalservices.com/blog-posts/driving-drive-drug-innovation-and-market-access-part-1-clinical-trial-cost-breakdown/ [https://perma.cc/2XLR-U8LJ]. An sNDA must contain these studies for the FDA to approve a new indication. *See* Rachel Sherman et al., *Considerations for Summary Review of Supplemental NDA/BLA Submissions in Oncology*, CONF. ON CLINICAL CANCER RES. 1 (2014), https://www.focr.org/sites/default/files/Considerations%20for%20Summary%20Review%20of%20Supplemental%20NDA%20BLA%20Submissions.pdf [https://perma.cc/A3U3-6B9M] ("A supplemental application typically parallels the content of an original NDA . . . application, and includes the 'raw' datasets . . . from clinical trials and efficacy and safety analyses derived from these data . . . .").

47. *Step 3: Clinical Research*, FDA, https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm [https://perma.cc/W9WZ-BV5B] (last visited Mar. 15, 2018) (finding that Phase 2 studies can last for up to 2 years and only 33 percent of drugs move past this stage; for Phase 3 studies, the length of time is one to four years and only 25 to 30 percent of drugs move to the next phase).

48. "[T]he term of a new patent is 20 years from the date on which the application for the patent was filed in the United States." *Frequently Asked Questions on Patents & Exclusivity*, FDA (Nov. 14, 2017), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm#howlongpatentterm [https://perma.cc/5XVU-8WHA]. Approval of an sNDA grants a three-year product exclusivity period for the applicant, which can stretch beyond the twenty-year patent exclusivity period. New Drug Product Exclusivity, 21 C.F.R. § 314.108(b)(5) (2018).

seek FDA approval before selling a drug for an off-label use.[49] Finally, generic competition will likely eat into profits once the patent protection and exclusivity periods expire.[50] While the costs of approving new uses clearly incentivizes manufacturers to promote off-label uses, regulation of these off-label uses raises separate free speech issues.

B. The First Amendment and Off-Label Promotion

Government restrictions on the speech used in off-label promotion can violate the First Amendment.[51] The First Amendment will not always invalidate these regulations, however—different types of speech merit different levels of protection.[52] At issue in the FDA's regulation of off-label drug promotion is commercial speech. The Supreme Court has defined commercial speech as "speech that does no more than propose a commercial transaction."[53] The government is constitutionally permitted to regulate this speech in certain situations.[54] However, the ability to regulate commercial speech is not absolute,[55] and the *Central Hudson* test is used to evaluate government restrictions on this type of speech.[56]

The *Central Hudson* test is applicable when the FDA restricts truthful, nonmisleading speech.[57] It must be considered both for FDA restrictions that

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49. Due to the time necessary for drug development, the average market-exclusivity period for drugs before generic competition begins is less than fourteen years. Henry Grabowski et al., *Updated Trends in US Brand-Name and Generic Drug Competition*, 19 J. MED. ECON. 836, 839 (2016).

50. *See id.* at 836 (noting that, "[a]fter generic entry, brands rapidly lost sales, with their average unit share being . . . 12% [of the] overall" market for the drug).

51. The relevant part of the First Amendment states that "Congress shall make no law . . . abridging the freedom of speech . . . ." U.S. CONST. amend. I.

52. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 562–63 (1980) ("The Constitution . . . accords a lesser protection to commercial speech than to other constitutionally guaranteed expression."); *see also* Victor Brudney, *The First Amendment and Commercial Speech*, 53 B.C. L. REV. 1153, 1153 (2012) ("[N]ot all expression is included in the speech whose freedom the First Amendment prohibits Congress from abridging.").

53. Harris v. Quinn, 134 S. Ct. 2618, 2639 (2014) (quoting United States v. United Foods, Inc., 533 U.S. 405, 409 (2001)). Another conception of commercial speech is "expression related solely to the economic interests of the speaker and its audience." *Cent. Hudson*, 447 U.S. at 561. Given that speech used in off-label promotion was treated as commercial speech in *United States v. Caronia* and *Washington Legal Foundation v. Friedman*, as well as numerous other cases, it seems safe to assume that off-label drug promotion is commercial speech for First Amendment purposes. *See infra* Part II.B.

54. *Cent. Hudson*, 447 U.S. at 563 ("[T]here can be no constitutional objection to the suppression of commercial messages that do not accurately inform the public about lawful activity.").

55. *See, e.g.*, *id.* ("The protection available for particular commercial expression turns on the nature both of the expression and of the governmental interests served by its regulation.").

56. The *Central Hudson* test has four steps. A court first asks whether the regulated speech concerns lawful activity and is not misleading. *Id.* at 566. If it concerns lawful activity and is not misleading, the next question is "whether the asserted governmental interest is substantial." *Id.* If the interest is substantial, then the court "must determine whether the regulation directly advances the governmental interest asserted, and whether it is not more extensive than is necessary to serve that interest" to decide whether the regulation is constitutional. *Id.*

57. *See supra* note 56.

facially restrict speech and for laws and regulations that are facially neutral but whose purpose is to suppress speech.[58] Furthermore, "[a]n individual's right to speak is implicated when information he or she possesses is subjected to 'restraints on the way in which the information might be used' or disseminated."[59] Finally, if a government restriction is directed at commerce and incidentally burdens speech, it does not violate the First Amendment.[60] Because the intended-use regulation allows the government to use speech in a misbranding action, thereby potentially restricting commercial speech, the regulation ought to be analyzed under *Central Hudson*.[61]

C. The Proposed Amendment to the Intended-Use Regulation

In the current version of the intended-use regulation, "*intended use*[] . . . refer[s] 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."[62] In 2015, the FDA proposed amending the rule in response to the Family Smoking Prevention and Tobacco Control Act to clarify when a product made or derived from tobacco should be classified as a drug or a device, rather than as a tobacco product.[63] The original proposed change to the regulation eliminated its last sentence, which reads, "if a manufacturer knows . . . that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it," then the drug must have adequate directions for use for this other use.[64] Under the proposed amendment, the FDA "would not regard a firm as intending an unapproved new use for an approved or cleared medical product

58. Sorrell v. IMS Health Inc., 564 U.S. 552, 566 (2011).

59. *Id.* at 568 (quoting Seattle Times Co. v. Reinhart, 467 U.S. 20, 32 (1984)). The statute at issue in *Sorrell* facially restricted pharmacies from selling prescriber-identifying information in their possession. *Id.* at 552. For the full wording of the statute, see *infra* note 121.

60. *Sorrell*, 564 U.S. at 567.

61. If a restriction on speech fails the *Central Hudson* test, then the limitation is unconstitutional. *See Cent. Hudson*, 447 U.S. at 571 ("In the absence of a showing that more limited speech regulation would be ineffective, we cannot approve the complete suppression of Central Hudson's advertising.").

62. Meaning of "Intended Uses," 21 C.F.R. § 201.128 (2018).

63. *See* Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 80 Fed. Reg. 57,756, 57,756 (proposed Sept. 25, 2015) (to be codified at 21 C.F.R. pts. 201, 801, 1100) ("Because some ambiguity surrounds the circumstances under which a product that is made or derived from tobacco would be regulated as a drug, device, or combination product . . . FDA is initiating this rulemaking . . . ."). The rule change was prompted by the newly added category of tobacco products to the FDCA, which is defined as "any product made or derived from tobacco that is intended for human consumption." *Id.* at 57,757. The definition excludes drugs, devices, or combinations of drugs and devices. *Id.* Since drugs and devices are defined, in part, by their intended uses, how to find a product's intended use helps to determine whether it should be regulated as a drug, device, or tobacco product. *Id.*

64. 21 C.F.R. § 201.128.

based solely on the firm's knowledge that such product was being prescribed or used by doctors for such use."[65]

The comment period of the rule originally extended until November 24, 2015.[66] After receiving 1717 comments on the proposed rule change,[67] the FDA extended the comment period until December 30, 2015.[68] The FDA then received 226 additional comments.[69] After further delay, the FDA finally released the final version of the regulation.[70] However, the controversy over the rule would not end here—in the proposed final rule, the FDA replaced the knowledge clause with a new "totality of the evidence standard" instead of simply eliminating it, as was originally proposed.[71]

According to the FDA, the totality of the evidence standard merely reflects the FDA's long-standing approach regarding what types of evidence it can use to find a drug's intended use.[72] The FDA views the amendment as not changing its regulatory approach.[73] The industry reaction to the new

65. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 80 Fed. Reg. at 57,757.

66. *Id.* at 57,756.

67. *Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses,"* REGULATIONS.GOV, https://www.regulations.gov/document?D=FDA-2015-N-2002-0001 [https://perma.cc/Y5WF-BWU3] (last visited Mar. 15, 2018).

68. *See* Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"; Reopening of the Comment Period, 80 Fed. Reg. 74,737, 74,737 (Nov. 30, 2015) (to be codified at 21 C.F.R. pts. 210, 801, 1100).

69. *Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"; Reopening of the Comment Period*, REGULATIONS.GOV, https://www.regulations.gov/document?D=FDA-2015-N-2002-0008 [https://perma.cc/2MBV-VKRB] (last visited Mar. 15, 2018).

70. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2193 (proposed Jan. 9, 2017) (to be codified at 21 C.F.R. pts. 201, 801, 1100).

71. *Id.* at 2205–06 ("[I]f the totality of the evidence establishes that a manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used [for off-label purposes] . . . he is required . . . to provide for the drug adequate labeling that accords with such other intended uses."). The controversy is far from over. As of the date of publication of this Note, the FDA, after delaying the amendment's effective date multiple times, has proposed to delay its implementation until further notice. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses"; Proposed Partial Delay of Effective Date, 83 Fed. Reg. 2092, 2093 (proposed Jan. 16, 2018) (to be codified at 21 C.F.R. pts. 201, 801, 1100) (discussing how the FDA delayed the effective date of the rule twice before proposing to delay it yet again).

72. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. at 2204 ("These changes do not reflect a change in FDA's approach regarding evidence of intended use for drugs . . . .").

73. *Id.* at 2205. Specifically, the totality of the evidence standard is partially meant to show that the FDA will not deem a manufacturer's mere knowledge of a drug being used for an unapproved use as the manufacturer intending the drug be used for that use. *Id.* at 2206.

standard, however, was sharp and reflected a fear that the standard will be used to expand the circumstances under which the FDA can determine a new intended use for a drug (and therefore deem it misbranded for lacking adequate directions for use).[74] To industry commentators, the First Amendment and the case law interpreting it protect truthful speech so that it cannot be used in a misbranding case.[75]

II. DIFFERENT VIEWS ABOUT USING SPEECH IN THE REGULATION OF OFF-LABEL PROMOTION

Courts generally hold that the FDA can find an intended use based on the circumstances surrounding a drug's sale,[76] "promotional claims, advertising, *and any other relevant source*."[77] Furthermore, under the *Central Hudson* test, the government can constitutionally use nontruthful or misleading speech in off-label promotion as part of a misbranding charge.[78] It is unclear, however, to what extent the government may use truthful, nonmisleading speech in off-label drug promotion to prove a misbranding crime.

The Second Circuit's decision in *United States v. Caronia* is seen by many as a pivotal case for off-label promotion.[79] It holds that the FDA cannot criminalize truthful, nonmisleading speech.[80] While at first blush this may seem to categorically prevent the FDA from using such speech in a misbranding case, later courts have been divided. Some, including the Second Circuit in post-*Caronia* decisions, have held that while the FDA

However, in the new regulation, knowledge of a drug being used for off-label uses can be *part* of the evidence used to find a new intended use for a drug. *Id.*

74. For example, some comments to the proposed rule wanted the FDA to contract its definition of intended use due to First Amendment constraints on regulating truthful speech. *Id*. at 2208–09. Other commentators cite to *Caronia* to argue that the "totality of the evidence standard" raises First Amendment concerns. Letter from Paul E. Kalb et al., *supra* note 24, at 19–21; *see also supra* note 20.

75. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. at 2208–09 ("One comment stated that, under *Central Hudson* . . . government regulation of truthful speech concerning unlawful activity violates the First Amendment unless government regulators can [satisfy the *Central Hudson* test] . . . . [A]nother comment urged FDA to confirm that truthful and non-misleading speech cannot form the basis of a manufacturer's intended use of a medical product."); *see also supra* note 20.

76. *See, e.g.*, United States v. Travia, 180 F. Supp. 2d 115, 119 (D.D.C. 2001).

77. Hanson v. United States, 417 F. Supp. 30, 35 (D. Minn.) (emphasis added), *aff'd*, 540 F.2d 947 (8th Cir. 1976); *see also* Action on Smoking & Health v. Harris, 655 F.2d 236, 239 (D.C. Cir. 1980); Nat'l Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 334 (2d Cir. 1977).

78. See *supra* note 56 for a discussion of the *Central Hudson* test.

79. Marcia M. Boumil & Kaitlyn L. Dunn, *Off-Label Marketing of Pharmaceutical Products in the Wake of* United States v. Caronia *and* United States v. Harkonen, 9 J. HEALTH & BIOMED. L. 385, 430 (2014) (discussing that commentators originally predicted that *Caronia* would have a large influence on the FDA's regulation of off-label marketing); Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545, 552 (2014) ("FDA's regulatory regime for off-label promotion suffered a severe blow in the . . . case of *United States v. Caronia* . . . ."); *see also supra* note 20 (discussing industry objections to the amendment to the intended-use regulation). *But see supra* note 13 (discussing *Caronia*'s limited geographic reach).

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

cannot criminalize truthful, nonmisleading speech, it can use such speech as evidence of a drug's intended use.[81] Other courts decline to follow *Caronia* and hold that this type of speech can underlie a misbranding charge.[82]

Part II.A provides an overview of the types of evidence that the government can permissibly use to find a drug's intended use in a misbranding action. Part II.B then examines First Amendment restrictions on the government using truthful, nonmisleading speech to prove that a drug was sold without adequate directions for use. Part II.C then considers post-*Caronia* decisions that suggest that the government can permissibly utilize truthful speech in certain situations to secure a conviction.

A. The FDA Can Use a Wide Variety of Evidence in a Misbranding Case

In *Whitaker v. Thompson*,[83] the court held that the FDA can use the speech in an article's labeling to find its intended use.[84] There, the plaintiff attempted to sell the dietary supplement saw palmetto extract with a label claiming that it could treat benign prostatic hyperplasia (BPH).[85] The FDA said that this claim would render saw palmetto extract an unapproved new drug, as it would be intended by the manufacturer to treat BPH, which the supplement was not approved for.[86] The U.S. Court of Appeals for the District of Columbia agreed with the FDA and held that that the First Amendment allows "the FDA to use speech, *in the form of labeling*, to infer intent for purposes of determining that Whitaker's proposed sale of saw palmetto extract would constitute the forbidden sale of an unapproved drug."[87]

In reaching this conclusion, the *Whitaker* court rejected the appellant's argument that the government violated the First Amendment by construing the FDCA to criminalize truthful speech.[88] Instead, the court held that claims that a manufacturer makes about a product help to determine whether the product is a drug when the claims relate to the product's intended use.[89] Therefore, the government appropriately determined that the speech on the label was evidence of the intent to sell saw palmetto extract as a drug.[90] According to the court, using speech as evidence of intent does not violate the First Amendment, even when doing so "renders an otherwise permissible

81. *See infra* Part II.C.

82. *See infra* Part II.C. This circuit split is likely to last for the foreseeable future, as the FDA "is evidently concerned by the prospect that the Supreme Court would limit its regulatory authority if the question of off-label promotion ever came before it," which explains the lack of recent FDA enforcement action over off-label promotion. Comanor & Needleman, *supra* note 13, at 133.

83. 353 F.3d 947 (D.C. Cir. 2004).

84. *Id.* at 953.

85. *Id.* at 948.

86. *Id.* at 948–49; *see also supra* notes 25–38 and accompanying text.

87. *Whitaker*, 353 F.3d at 953 (emphasis added); *see supra* note 27 (defining labeling).

88. *Whitaker*, 353 F.3d at 953.

89. *See id.*

90. *See id.*

act unlawful."[91] Based on this analysis, the court found that the FDA's use of the label's claim to determine that selling saw palmetto extract would constitute an illegal sale of an unapproved drug was constitutional.[92]

Furthermore, the FDA has not been historically limited to speech in an article's labeling to establish its intended use. In fact, the intended use of a product "is determined from its label, accompanying labeling, promotional claims, advertising, *and any other relevant source*."[93] This has allowed the FDA to, for example, find that selling nitrous oxide outside a concert makes the nitrous oxide an unapproved drug, even without any labeling on the nitrous oxide, based on the circumstances of sale indicating that the gas was intended to affect the structure of the human body.[94] It has also allowed the FDA to deem vitamins sold at certain dosages drugs, instead of food, because vitamins sold at the levels offered by the manufacturer were used almost exclusively for medical reasons and had no known nutritional uses.[95]

The FDA has also usually been allowed to use speech in off-label promotion to find a drug's intended use. In fact, *Caronia* cites a number of cases where "[t]he government . . . prosecuted—and obtained convictions against—pharmaceutical companies and their representatives for misbranding based on their off-label promotion."[96] For example, GlaxoSmithKline pled guilty to a misbranding crime for promoting the drug Paxil to treat depression in patients under eighteen years old, an unapproved population, and for promoting the drug Wellbutrin to treat sexual dysfunction, drug addiction, and ADHD when Wellbutrin was approved to treat only major depressive disorder.[97] Clearly, the government can use speech in off-label promotion to prove misbranding. The question is to what the extent the government may do so.

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91. *Id.* The court noted that "the First Amendment allows 'the evidentiary use of speech to establish the elements of a crime or to prove motive or intent'" to support this finding. *Id.* (quoting Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993)).

92. *See id.* Under the *Central Hudson* test, the government can ban speech concerning unlawful activity. *See supra* note 56.

93. Hanson v. United States, 417 F. Supp. 30, 35 (D. Minn.) (emphasis added), *aff'd*, 540 F.2d 947 (8th Cir. 1976); *see also supra* note 77.

94. *See* United States v. Travia, 180 F. Supp. 2d 115, 116–117, 119 (D.C. Cir. 2001). The court specified that "[t]his case is obviously unique in that . . . the sellers did not need to label or advertise their product, as the environment provided the necessary information between buyer and seller." *Id.* at 119.

95. Nat'l Nutritional Foods Ass'n v. Mathews, 557 F.2d 325 (2d Cir. 1977). Today, vitamins are considered dietary supplements for FDA regulatory purposes. At the time *National Nutritional Foods Association* was decided, the dietary supplement category did not exist; it was created in 1994. *See* Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 3, 108 Stat. 4325, 4372.

96. United States. v. Caronia, 703 F.3d 149, 154 (2d Cir. 2012).

97. Press Release, U.S. Dep't of Justice, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012), https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report [https://perma.cc/7TN9-LHH8].

B. Caronia*'s Limitation on Using Truthful, Nonmisleading Speech in a Misbranding Case*

While the FDA has wide leeway to use a drug manufacturer's or its representative's speech and conduct to determine a drug's intended use, its ability to do so based on truthful, nonmisleading communications and to then bring a misbranding charge has recently come into question. The *Caronia* decision is central to the claim that the FDA is limited in using such speech in a misbranding prosecution. Part II.B.1 looks at a pre-*Caronia* decision that holds that the FDA cannot restrict the release of truthful, nonmisleading information. Part II.B.2 considers *Caronia* in detail, and Part II.B.3 examines a later decision's explanation of *Caronia*.

1. An Early Assault on the FDA's Regulation of Off-Label Drug Promotion

Washington Legal Foundation v. Friedman[98] is a pre-*Caronia* case that limited the FDA's ability to use truthful speech in a misbranding prosecution. In that case, one FDA guidance document limited manufacturers from holding continuing medical education conferences that discussed off-label uses of otherwise approved drugs.[99] Another guidance document limited drug manufacturers from distributing textbook excerpts and article reprints from medical journals that address off-label uses.[100] The court held that the seminars and written material were commercial speech. As such, restrictions on their dissemination must be analyzed under First Amendment jurisprudence.[101] The restrictions were then struck down under the *Central Hudson* test.[102]

On appeal, the case was vacated.[103] This happened after the FDA changed its interpretation of the FDCA and guidance documents. It said that complying with the guidance documents' requirements created a safe harbor, which would protect manufacturers from having certain forms of speech used against them by the FDA in misbranding actions; this safe harbor stood in contrast to the existing policy whereby the FDA could restrict or sanction such speech.[104] In vacating the case, the court specified that "the FDA retains the prerogative to use both types of arguably promotional conduct as *evidence* in a misbranding or 'intended use' enforcement action."[105] While the case has no precedential value, its holding that the FDA cannot restrict truthful, nonmisleading speech would later reappear in a similar situation.

98. 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated in part sub nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).
99. *See Wash. Legal Found.*, 13 F. Supp. 2d at 57–58.
100. *Id.* at 58.
101. *Id.* at 59–60.
102. *Id.* at 65–73. Both guidance documents were targeted at truthful, nonmisleading speech. *Id.* at 65–69.
103. *Wash. Legal Found.*, 202 F.3d at 337.
104. *See id.* at 335.
105. *Id.* at 336.

2. *Caronia* Revitalizes the Limitation on FDA Regulation of Off-Label Drug Promotion

The principle from *Washington Legal Foundation* that the FDA cannot criminalize truthful, nonmisleading speech resurfaced in *United States v. Caronia*.[106] In *Caronia*, Orphan Medical hired Alfred Caronia to promote the drug Xyrem.[107] The FDA approved Xyrem to treat narcolepsy patients who also suffer from cataplexy, as well as "narcolepsy patients with excessive daytime sleepiness."[108] Caronia was recorded promoting the drug for various off-label uses to prospective prescribers, including promoting Xyrem for patients under sixteen years old, for whom the drug is not approved.[109] The jury found Caronia guilty of conspiring to introduce a misbranded drug into interstate commerce.[110]

The Second Circuit vacated Caronia's conviction.[111] The majority found that "the government and the FDA have construed the FDCA's misbranding provisions to prohibit off-label promotion by pharmaceutical manufacturers."[112] The majority held such a construction unconstitutional under the *Central Hudson* test.[113] In finding that the government construed the FDCA to criminalize speech (instead of using speech as evidence of the intent to commit a misbranding crime), the court first pointed to an FDA draft guidance document that stated that "[a]n approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'"[114]

The majority then focused on the government's conduct at trial to show that Caronia was prosecuted for his speech. For example, the court noted that the government repeatedly argued that mere off-label promotion constitutes criminal conduct.[115] The court also discussed the fact that "[t]he government

106. 703 F.3d 149 (2d Cir. 2012).

107. *Id.* at 155–56.

108. *Id.* at 155.

109. *Id.* at 156–57.

110. *Id.* at 159. Caronia was convicted under 18 U.S.C. § 371(a) and 21 U.S.C. § 331(a). *Id.*; *see supra* notes 37–38 and accompanying text.

111. *Caronia*, 703 F.3d at 169.

112. *Id.* By contrast, the government contended that it did not construe the FDCA to criminalize speech—instead, it claimed that it used the speech as evidence of the intent to sell Xyrem for off-label uses, meaning that it was sold without adequate directions for use. *Id.* at 160–61.

113. The court found that this construction of the FDCA both did not directly advance substantial government interests and was not narrowly tailored to achieving them. *Id.* at 166–69.

114. *Id.* at 155 (alteration in original) (quoting *Guidance for Industry: 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), https://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm [https://perma.cc/WLX3-SGL7].

115. *Id.* at 161. The government argued, for example, that "[Caronia] knew the rules: you can't promote and market Xyrem for uses that have not been approved by the FDA" because "[t]hat's misbranding. That's promoting and marketing a drug by a pharmaceutical company representative for [unapproved uses]." *Id.* at 158 (statements of government counsel from the record).

never argued . . . that the promotion was evidence of intent . . . . The government never suggested . . . that Caronia conspired to place false or deficient labeling on a drug."[116] Finally, the jury instructions made it clear that Caronia was convicted for his speech in violation of the First Amendment.[117] The *Caronia* majority concluded that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[118] To the court, the government erred because its "theory of prosecution identified Caronia's speech alone as the proscribed conduct."[119]

The majority based its finding that the government unconstitutionally burdened speech on *Sorrell v. IMS Health Inc.*[120] In *Sorrell*, a Vermont statute prohibited the sale, disclosure by pharmacies for marketing use, and use by pharmaceutical manufacturers of information revealing the prescribing practices of doctors.[121] In holding the statute unconstitutional, the Court argued that the law facially imposed content- and speaker-based restrictions on commercial speech.[122] It was content based because it disfavored, for example, speech used in marketing (as opposed to using the information for educational purposes), and it was speaker based because it disfavored certain speakers, such as pharmaceutical manufacturers.[123] Because the statute imposed these restrictions on speech, it was subject to *Central Hudson* scrutiny, which it failed.[124]

The *Caronia* majority applied *Sorrell* to find that the government construed the FDCA's misbranding provisions to impose content- and speaker-based restrictions on speech.[125] The construction was content-based

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116. *Id.* at 161.

117. The district court's jury charge stated that a "misbranded drug may be shown by a promotion of the drug by a distributor for an intended use different from the use for which the drug was approved by the [FDA]." *Id.* at 159 (alteration in original). The majority opinion also noted that "the district court flatly stated to the jury that pharmaceutical representatives are prohibited from engaging in off-label promotion." *Id.* at 161.

118. *Id.* at 169.

119. *Id.* at 159.

120. 564 U.S. 552 (2011).

121. *Id.* at 557. The full statute states:

> A health insurer, a self-insured employer, an electronic transmission intermediary, a pharmacy, or other similar entity shall not sell, license, or exchange for value regulated records containing prescriber-identifiable information, nor permit the use of regulated records containing prescriber-identifiable information for marketing or promoting a prescription drug, unless the prescriber consents . . . . Pharmaceutical manufacturers and pharmaceutical marketers shall not use prescriber-identifiable information for marketing or promoting a prescription drug unless the prescriber consents . . . .

Id. at 558–59. The penalties for violating the statute were not criminal. *Id.* at 559.

122. *Id.* at 563–64.

123. *Id.* at 564.

124. *See id.* at 566, 571–72.

125. United States v. Caronia, 703 F.3d 149, 164 (2d Cir. 2012). The court applied the *Central Hudson* test, even though *Sorrell* was not clear as to what level of heightened scrutiny applies when a government regulation on commercial speech is content- and speaker-based. *Id.* at 164–65.

because "speech about the government-approved use of drugs is permitted, while certain speech about the off-label use of drugs . . . is prohibited."[126] It was speaker-based because it targets pharmaceutical manufacturers, while others do not have their speech restricted.[127] Based on these restrictions, the statute was subject to the *Central Hudson* test, under which it was found to violate the First Amendment.[128]

The opinion in *Caronia* was not unanimous. In her dissent, Judge Debra Livingston, rather than finding that the government prosecuted Caronia for his speech, characterized the government's use of Caronia's speech as mere evidence of Xyrem's intended use.[129] She disagreed that the jury instructions told the jury that Caronia could be convicted for his speech alone. Rather, she argued that the instructions, taken as a whole, explained that Caronia could be convicted only for a conspiracy to introduce a misbranded drug into interstate commerce.[130] She noted that speech alone was insufficient to convict Caronia—rather, "if the jury had concluded there was a reasonable doubt as to whether Caronia . . . intended to . . . introduce [Xyrem] into interstate commerce—then Caronia could not have been convicted . . . no matter what he said."[131] Judge Livingston compared the case to *Whitaker* to emphasize that the FDA could use speech as evidence of a drug's intended use without running afoul of the First Amendment—that is, that the *Central Hudson* test was not needed.[132] Given the lack of unanimity in *Caronia*, a later decision examining it is useful to determine what it truly stands for.

3. *Amarin* Elaborates on *Caronia* and Explains Its Interaction with the Elements of a Misbranding Crime

Caronia was analyzed in *Amarin Pharma, Inc. v. FDA*.[133] In *Amarin*, the FDA refused a manufacturer's request to approve the drug Vascepa for a new indication.[134] The drug was originally approved to treat patients with triglyceride levels above 500 mg/dL[135] of blood; Amarin sought further approval for Vascepa to treat those with triglyceride levels between 200 and 499 mg/dL of blood.[136] The FDA communicated to Amarin that it would

126. *Id.* at 165.
127. *Id.*
128. *See id.* at 164.
129. *See id.* at 172 (Livingston, J., dissenting) ("I disagree that the government prosecuted Caronia for his speech.").
130. *See id.* at 173.
131. *Id.* at 176.
132. *See id.* at 177. Judge Livingston then proceeded to apply the *Central Hudson* test in the event that using speech as evidence of intent is not necessarily constitutionally permissible. *Id.* She found that the use of speech as evidence of the intent to commit a crime did not violate the First Amendment in *Caronia*. *Id.* at 177–81.
133. 119 F. Supp. 3d 196 (S.D.N.Y. 2015).
134. *Id.* at 211–12.
135. "Mg/dL" means milligrams per deciliter. It "is a measurement that indicates the amount of a particular substance . . . in a specific amount of blood." *What Does Mg/dL Mean*, WebMD (Jan. 20, 2017), https://www.webmd.com/diabetes/qa/what-does-mgdl-mean [https://perma.cc/58LN-BW75].
136. *Amarin*, 119 F. Supp. at 209.

deem Vascepa misbranded if the manufacturer marketed the drug for use in those with the lower triglyceride levels before approval of its sNDA.[137] The information that Amarin relied on in requesting approval—and that it would convey to doctors—for the unapproved use consisted of truthful information derived from studies requested by the FDA, which showed that Vascepa did indeed reduce triglyceride levels in those with levels between 200 and 499 mg/dL of blood.[138] The FDA rejected the sNDA, despite the triglyceride level reduction, because there was no evidence that the reduction lowered the risk of cardiovascular issues.[139]

In *Amarin*, Judge Paul Engelmayer relied on *Caronia* to hold that the FDA could bring a misbranding action, or threaten to do so, based solely on truthful speech used in off-label promotion.[140] Holding that *Caronia* was not limited to its facts,[141] Judge Engelmayer read *Caronia* to mean that speech could be used to find the intent to commit a misbranding offense, but it could not be the actus reus in a criminal misbranding allegation.[142] For example, speech can be used as evidence of the intent to commit a misbranding crime if the promotion consisted of more than just speech, like paying doctors money or buying them expensive vacations.[143] To this court, "*Caronia* does not limit the Government's ability to use promotional speech to establish intent in a misbranding action with a proper actus reus."[144] This interpretation appears to be supported by post-*Caronia* Second Circuit decisions and opinions from other courts.

C. How Far Does Caronia*'s Prohibition on Using Speech in a Misbranding Case Extend?*

Caronia has not been universally accepted as categorically preventing the FDA from using truthful, nonmisleading speech in a misbranding case. This position is seen in the Second Circuit, which issued the *Caronia* opinion. For example, in *United States v. Kaziu*,[145] the Second Circuit cited to *Caronia* to show that where jury instructions specify that speech shows only a mental state and is not on trial, the First Amendment does not prevent that speech from being used to prove an element of a crime.[146] While *Kaziu* was

137. *See id.* at 212. For a discussion of the sNDA, see *supra* notes 44–49 and accompanying text.
138. *Amarin*, 119 F. Supp. 3d at 211.
139. *Id.* at 211–12.
140. *Id.* at 224.
141. *Id.*
142. *Id.* at 227–28.
143. *Id.* at 228.
144. *Id.*
145. 559 F. App'x 32 (2d Cir. 2014).
146. *Id.* at 35. *Kaziu* was an appeal from a conviction for providing material support to a foreign terrorist organization and for various conspiracies. *Id.* at 34–35. The Second Circuit allowed speech to be used to prove the defendant's mental state when the jury instructions specified that the defendant was not on trial for his extremist views and that the speech indicating such views was not sufficient to find the defendant guilty without proof beyond a reasonable doubt that the defendant conspired to provide material support to a terrorist organization and conspired to murder in a foreign country. *Id.* at 35–36.

nonprecedential, a later case, *United States ex rel. Polansky v. Pfizer, Inc.*,[147] indicates that the Second Circuit does not view *Caronia* as categorically preventing the use of truthful speech in a misbranding case. In that decision, the court specified that "*Caronia* left open the government's ability to prove misbranding on a theory that promotional speech provides evidence that a drug is intended for [an off-label] use."[148]

District courts in the Ninth Circuit also tend to agree that truthful, nonmisleading speech can be used to prove a misbranding crime. These opinions rest on the holding of *Carson v. Depuy Spine, Inc.*[149] While that case is nonprecedential and used the FDCA as the predicate violation for a negligence per se theory, the court held that promoting a "Class III" medical device[150] for an unapproved use violates the FDCA.[151] Although *Carson* was decided before *Caronia*, the district courts in the Ninth Circuit have had ample opportunity to evaluate off-label drug promotion post-*Caronia*. These courts have not come to a unanimous decision about whether *Caronia* prevents the FDA from using truthful, nonmisleading speech in a misbranding case.[152] However, the majority of courts within the circuit hold that the FDCA prohibits off-label promotion.[153]

Courts of other jurisdictions have also considered off-label promotion in light of *Caronia*. For example, in *Markland v. Insys Therapeutics, Inc.*,[154] the Middle District of Florida noted that "it is generally accepted that a manufacturer's off-label promotion of a drug runs afoul of federal law."[155] In so holding, the court noted that there is currently no consensus about whether the FDCA prohibits off-label promotion.[156]

147. 822 F.3d 613 (2d Cir. 2016).

148. *Id.* at 615 n.2.

149. 365 F. App'x 812 (9th Cir. 2010).

150. Medical devices are not discussed in this Note, but the same intended-use analysis applies to drugs and medical devices. *See* Gregory Gentry, *Criminalizing Knowledge: The Perverse Implications of the Intended Use Regulations for Off-Label Promotion Prosecutions*, 64 FOOD & DRUG L.J. 441, 442 (2009) ("Intended use is defined similarly for both drugs and medical devices.").

151. *Carson*, 365 F. App'x at 815.

152. *See, e.g.*, Schuler v. Medtronic, Inc., No. 14-cv-00241-R, 2014 WL 988516, at *1 (C.D. Cal. Mar. 12, 2014) ("[F]ederal law does not bar off-label promotion . . . .").

153. *See, e.g.*, United States v. Celgene Corp., 226 F. Supp. 3d 1032, 1038 n.3 (C.D. Cal. 2016) ("[I]t is generally viewed that off-label marketing is unlawful."); Jones v. Medtronic, 89 F. Supp. 3d 1035, 1058 (D. Ariz. 2015) ("This Court agrees with 'the majority of courts in [the Ninth] Circuit which have determined that the FDCA prohibits off-label promotion . . . .'" (quoting Beavers-Gabriel v. Medtronic, Inc., 15 F. Supp. 3d 1021, 1034 (D. Haw. 2014))); Hawkins v. Medtronic, Inc., No. 13-cv-00499, 2014 WL 346622, at *7 (E.D. Cal. Jan. 30 2014) ("The Ninth Circuit has considered [off-label promotion under the FDCA] and found that off-label promotion is unlawful. . . . Although [*Carson v. Depuy Spine, Inc.* is] not binding, this Court finds the Ninth Circuit's reasoning persuasive.").

154. 270 F. Supp. 3d 1318 (M.D. Fla. 2017).

155. *Id.* at 1325.

156. *Id.* at 1326 n.4. The court discussed that while *Caronia* prevents the FDCA from criminalizing speech in a misbranding criminal prosecution, the Ninth Circuit does not universally take such a view. *Id.* The court also noted that a Southern District of Texas decision discusses the lack of clarity over whether truthful off-label promotion is banned by the FDA, as opposed to only false and/or misleading off-label promotion. *Id.*

III. CAN THE FDA USE TRUTHFUL, NONMISLEADING SPEECH IN A MISBRANDING CASE?

Caronia clearly limits the FDA's ability to use truthful, nonmisleading speech in a misbranding case. However, it is unclear how broad this limitation is. Since *Caronia* focused on the jury believing that the FDCA bans off-label promotion and the law challenged in *Sorrell* restricted speech based on its speaker and content, this Part argues that the government is not completely barred from using truthful, nonmisleading speech in a misbranding case. It argues that the government may use this speech as long as it is not criminalized and is not the only evidence used to prove a misbranding offense. Part III.A contends that *Caronia* does not prohibit the use of truthful, nonmisleading speech in a misbranding case and is instead the product of the unique circumstances of that case. Part III.B argues that the new intended-use regulation does not facially violate the First Amendment, while Part III.C discusses how the FDA can carry out the amended regulation without raising an as-applied issue.

A. Caronia *Does Not Prevent the FDA from Using Truthful, Nonmisleading Speech as Evidence in a Misbranding Case*

Caronia focused on the jury believing that Alfred Caronia could be convicted of a conspiracy to introduce a misbranded drug into interstate commerce based solely on his off-label promotion.[157] When viewed in light of the FDA's historical ability to use a wide variety of evidence to find a drug's intended use, *Caronia* should not be construed as categorically banning the government from using truthful, nonmisleading speech to prove a misbranding offense. *Sorrell* dictates that this type of speech cannot be the only evidence used to convict one of a conspiracy to introduce a misbranded drug into interstate commerce. But, it does not prevent the government from using speech in off-label promotion as part of the evidence to prove such a conspiracy. Part III.A.1 examines *Caronia* in light of the cases that allow the FDA to use a wide variety of information to determine a drug's intended use. Part III.A.2 then argues that *Caronia* applied *Sorrell* to invalidate Caronia's conviction because of how the government argued its case and the trial court's jury instructions. Next, Part III.A.3 considers the implications of *Amarin*'s discussion of *Caronia*.

1. *Caronia* Breaks with a Long Line of Cases That Allow the Government to Use Any Relevant Source to Determine a Drug's Intended Use

Caronia breaks with the long-standing idea that the government can use a drug's "label, accompanying labeling, promotional claims, advertising, and any other relevant source" to find its intended use.[158] The cases supporting this proposition have allowed the government to determine a drug's intended

157. *See supra* notes 115–19 and accompanying text.

158. Hanson v. United States, 417 F. Supp. 30, 35 (D. Minn.), *aff'd*, 540 F.2d 947 (8th Cir. 1976); *see also supra* note 77.

use both from claims made about the product and from the circumstances of sale.[159] Based on this precedent, *Caronia* cannot mean that the government is always barred from using truthful speech in a misbranding case.[160]

First, in *Caronia*, the government used speech that made claims about a drug to find its intended use, which is analogous to *Whitaker*, where the court looked to claims in a drug's label to determine the drug's intended use.[161] Furthermore, the circumstances of *Caronia* (a drug representative discussing off-label uses with a prospective doctor-purchaser of Xyrem) indicate that the discussion was meant to promote Xyrem for off-label uses. This is similar to *United States v. Travia*,[162] where the circumstances of selling nitrous oxide outside of a concert allowed the FDA to find that the gas was intended to be used as a drug.[163]

These are but a few of the cases in which the FDA used a wide range of information, including speech, to find a drug's intended use.[164] In fact, in *Caronia*, the Second Circuit recognized the government's repeated successful prosecutions of pharmaceutical companies and their representatives for off-label promotion.[165] Under these cases, the Second Circuit should have found that Caronia's prosecution was permissible. However, according to the court, *Sorrell* compelled it to find that Caronia's conviction violated the First Amendment.[166] The Second Circuit was correct in applying *Sorrell* but only because of the unique circumstances of *Caronia*.

2. *Sorrell* Dictated That Caronia's Conviction Be Overturned Because of How the Government Argued Its Case in *Caronia*

Caronia applied the *Sorrell* standard because the jury instructions and the way the government argued the case made it appear to the jury that the FDCA bans speech.[167] *Sorrell* involved a state law that facially restricted speech—once a certain speaker spoke certain information, that speaker was subject to civil penalties.[168] By contrast, the FDCA has no such provision.[169] Instead, the regulations implementing it merely allow the government to use speech as evidence of a drug's intended use. The intended use can then be used to support a misbranding charge only if the misbranded drug was introduced into interstate commerce or there was a conspiracy to do so.[170] Under the

159. *See supra* Part II.A.
160. *See supra* notes 27–39 and accompanying text.
161. *See supra* notes 83–92 and accompanying text.
162. 180 F. Supp. 2d 115 (D.C. Cir. 2001).
163. *Supra* note 94 and accompanying text; *see also supra* note 95 and accompanying text.
164. *See supra* note 77.
165. *See supra* note 96 and accompanying text.
166. *See supra* Part II.B.2.
167. United States v. Caronia, 703 F.3d 149, 161 (2d Cir. 2012) ("[T]he government's summation and the district court's instruction left the jury to understand that Caronia's speech was itself the proscribed conduct."); *see also supra* notes 115–17 and accompanying text.
168. *See supra* notes 121–24 and accompanying text.
169. *See supra* note 32 and accompanying text.
170. *See supra* Part I.A.

wording of the FDCA and its implementing regulations, speech is not criminalized.

That is not, according to *Caronia*, how the government construed the FDCA. *Caronia* focused on the government arguing that a crime occurs when a drug manufacturer or its representative promotes a drug for an off-label use.[171] It also discussed the jury instructions, which made it appear to the jury that it could convict Caronia of a crime based solely on his speech.[172] Therefore, *Caronia* applied the *Central Hudson* test because the majority viewed the government's construction of the FDCA to do what the statute in *Sorrell* did—to ban speech based on its speaker and content.[173] This view was not unanimously held in *Caronia*. Judge Livingston, who dissented, did not find that the government argued that the FDCA bans off-label promotion. Instead, she thought that the jury instructions made it clear that the FDCA contains no such prohibition and that speech was merely used as evidence of a crime, which does not violate the First Amendment.[174]

Given the focus of *Caronia* on the jury believing that the FDCA bans speech, it should not be interpreted as categorically prohibiting the government from using truthful speech in a misbranding prosecution. Its holding as applied to the facts of *Caronia* is correct, but it should be limited to situations where speech is criminalized based on its speaker and content (or appears to be to a jury), not where speech is used as evidence of a crime. The issue in *Caronia* was not the use of speech in a misbranding action—instead, it was the government's argument that speech alone allowed the jury to convict Alfred Caronia of a conspiracy to introduce a misbranded drug into interstate commerce.[175]

Therefore, had the government argued that speech was evidence of the intent to commit a misbranding offense and specified that speech alone could not convict Caronia, the case would no longer be akin to *Sorrell* because speech would not be restricted based on its speaker and content. This position is supported by the Second Circuit's post-*Caronia* decisions. By citing to *Caronia* and holding that it allows the government to prove misbranding by using promotional speech as evidence of a drug's intended use, the Second Circuit does not seem to agree that *Caronia* and *Sorrell* always prevent the government from using truthful, nonmisleading speech in a misbranding case.[176]

171. *See supra* notes 114–16 and accompanying text.

172. *See supra* note 117 and accompanying text.

173. United States v. Caronia, 703 F.3d 149, 164 (2d Cir. 2012) ("[W]e conclude that the government's construction of the FDCA's misbranding provisions imposes content- and speaker-based restrictions on speech . . . ."). See *supra* note 121 for the wording of the statute at issue in *Sorrell*.

174. *See supra* notes 129–32 and accompanying text.

175. *Caronia*, 703 F.3d at 161 ("[T]he government clearly prosecuted Caronia for his words—for his speech.").

176. *See supra* notes 145–48 and accompanying text.

3. *Amarin*'s Discussion of *Caronia* Suggests That *Caronia* Will Not Significantly Interfere with the Regulation of Off-Label Drug Promotion

Amarin holds that, under *Caronia*, truthful speech can support mens rea in a misbranding allegation, but it cannot be the actus reus.[177] Therefore, according to *Amarin*, when off-label promotion consists solely of truthful speech, the FDA cannot bring a misbranding charge against the speaker.[178] In such a situation, speech is effectively criminalized—it alone is sufficient to convict one of a misbranding offense.

This position is correct. Under the FDCA, the actus reus of a misbranding offense is the introduction of a drug into interstate commerce or a conspiracy to do so.[179] So, under the FDCA, the misbranding provisions do not hold that speech is criminalized. Speech does not, and cannot, result in a conviction without the actus reus of selling a drug into interstate commerce or conspiring to do so. This was the issue in *Caronia*—the government used speech as the actus reus to find a conspiracy to sell a misbranded drug.[180]

Amarin, therefore, found that *Caronia* means that truthful speech, without any other evidence, cannot be used to convict one of a conspiracy to sell a misbranded drug.[181] This should not significantly limit the government's ability to regulate off-label promotion through the intended-use regulation, however. Speech does not occur in a vacuum, and *Amarin* recognizes that truthful speech, combined with other evidence of a conspiracy, allows the government to successfully bring a misbranding case.[182]

B. The Amended Intended-Use Regulation Does Not, on Its Face, Violate the First Amendment

The amendment to the intended-use regulation does not facially violate the First Amendment. The regulation, unlike the law in *Sorrell*, does not criminalize speech—instead, it discusses the evidence the FDA can use to find a drug's intended use.[183] Therefore, unlike the statute in *Sorrell* and the government's construction of the FDCA in *Caronia*, the amended regulation does not impose content- and speaker-based restrictions on speech. Instead,

177. *See supra* note 142 and accompanying text.

178. *See supra* note 140 and accompanying text.

179. *See supra* notes 37–38 and accompanying text.

180. Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 227 (S.D.N.Y. 2015) ("[*Caronia*] turned on the *actus reus* requirement. And *Caronia*'s holding was that the FDCA's misbranding provisions cannot constitutionally criminalize, and therefore do not reach, the act of truthful and non-misleading speech promoting off-label use."); *see also supra* note 119 and accompanying text.

181. *Amarin*, 119 F. Supp. 3d at 228.

182. The court gave examples of when a proper actus reus is present, like if "a manufacturer paid doctors money or bought them resort vacations . . . to reward them for prescribing a drug for offlabel use." *Id.*

183. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. 2193, 2217 (proposed Jan. 9, 2017) (to be codified at 21 C.F.R. pts. 201, 801, 1100).

it is an evidentiary tool that allows the FDA to use speech to find a drug's intended use.

This is true of the "totality of the evidence" standard in the regulation. Manufacturers claim that the new standard can chill speech,[184] and in *Sorrell*, the Court held that a facially neutral law whose purpose is to chill speech must be analyzed under the First Amendment.[185] This issue does not arise under the amended intended-use regulation because the FDA has stated that the amendment will not change the FDA's approach to finding a drug's intended use. By doing so, it has alerted drug companies that the new regulation's purpose is not to criminalize speech.[186] So, there should be no fear that words alone will result in a criminal prosecution. Therefore, the "totality of the evidence" standard, before the FDA enforces it, does not implicate the First Amendment as it does not restrict speech.[187] However, given the success of an as-applied challenge in *Amarin* (and *Caronia* seems to be an as-applied challenge to how the government enforced the FDCA), the FDA must carry out the regulation with care to avoid the issue that it faced in *Caronia*.[188]

C. How Should the FDA Carry Out the Amended Intended-Use Regulation?

The government cannot argue that truthful speech that makes a drug misbranded under the intended-use regulation is sufficient for a misbranding conviction.[189] The court in *Caronia* ruled as it did because the jury believed that the FDCA restricts speech, and under *Sorrell*, restrictions on speech based on speaker and content are subject to *Central Hudson* scrutiny.[190] So, if the government argues, as it did in *Caronia*, that speech in off-label promotion is sufficient to convict one of a conspiracy to sell a misbranded drug,[191] it would be tantamount to arguing that speech is always restricted when a pharmaceutical company representative discusses off-label drug usage with a doctor. This is the type of content- and speaker-based restriction on speech that implicates the First Amendment under *Caronia* and *Sorrell*.[192]

184. Letter from Advanced Med. Tech. Ass'n, *supra* note 20, at 1 ("[T]he Final Rule will create substantial confusion . . . and could thereby chill crucial interactions . . . .").

185. Sorrell v. IMS Health Inc., 564 U.S. 552, 566 (2011) ("Even if the hypothetical measure on its face appeared neutral as to content and speaker, its purpose to suppress speech and its unjustified burdens on expression would render it unconstitutional.").

186. Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding "Intended Uses," 82 Fed. Reg. at 2204 ("The[] changes [to the intended-use regulation] do not reflect a change in FDA's approach regarding evidence of intended use for drugs . . . .").

187. *See supra* note 58 and accompanying text.

188. Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196, 212 (S.D.N.Y. 2015) ("[Amarin] brought an as-applied First Amendment challenge to FDA regulations that prohibit Amarin 'from making completely truthful and non-misleading statements about its product to sophisticated healthcare professionals' . . . .").

189. See *supra* notes 27–39 and accompanying text for a discussion of misbranding.

190. *See supra* notes 122–24 and accompanying text.

191. *See supra* notes 111–12 and accompanying text.

192. *See supra* notes 122, 125, 128 and accompanying text.

Therefore, it is crucial that the government make clear at trial that truthful, nonmisleading speech alone is not enough to convict in a misbranding case and cannot serve as the sole evidence of a conspiracy to introduce a misbranded drug into interstate commerce. The government should always tell a jury that the FDCA does not ban speech. It should also emphasize that even if a drug is misbranded because of off-label promotion, speech alone cannot prove a conspiracy to sell the drug. These precautions should prevent a court from finding that the government construed the FDCA to ban speech, which would likely violate the First Amendment.[193]

Furthermore, as explained by *Amarin*, speech cannot be the actus reus when the government alleges a conspiracy to introduce a misbranded drug into interstate commerce, even if the government does not argue that speech is criminalized.[194] One way the government may be able to find a proper actus reus is to make an argument about the circumstances of sale, like in *Travia*.[195] The circumstances of a sales representative discussing a drug's unapproved uses with a prospective doctor-purchaser of the drug (as seen in *Caronia*), combined with speech advocating off-label usage that makes the drug lack adequate directions for use, may be enough to convince a jury of a conspiracy to sell a misbranded drug. The actus reus of the conspiracy is the representative discussing off-label uses with a potential purchaser of the drug, with the speech also showing that the drug is misbranded and that the conversation occurred as part of the conspiracy.

However, *Travia* was decided before *Sorrell*, and *Sorrell* bars the government from using the identity of the speaker and how the recipient of the speech plans to use the speech (i.e., the content of the speech) as the sole evidence of a conspiracy to sell a misbranded drug.[196] Post-*Sorrell*, it appears that convicting a representative who engages in promotion based on speech alone is tantamount to imposing speaker- and content-based restrictions on speech. There will be a conviction under the intended-use regulation whenever a sales representative talks about off-label promotion with a doctor, even when the government did not argue that speech is criminalized. Therefore, the government must introduce evidence besides speech as the actus reus of a conspiracy to introduce a misbranded drug into interstate commerce.[197]

It should not be difficult for the government to find a proper actus reus in many cases. Certain actions besides speech are clearly sufficient to serve as the actus reus of a conspiracy. For example, *Amarin* noted that if a manufacturer pays doctors money or buys them resort vacations in

193. Whether the restriction is unconstitutional is based on an application of the *Central Hudson* test. However, since such a construction failed the test in *Caronia* and content- and speaker-based restrictions on speech failed the test in *Sorrell* and in *Washington Legal Foundation*, it seems safe to assume that a future construction of the FDCA to ban truthful speech would also pose a high likelihood of being found unconstitutional. *See supra* Parts II.A–B.

194. *See supra* notes 140–44 and accompanying text.

195. *See supra* note 94 and accompanying text.

196. *See supra* notes 121–23 and accompanying text.

197. *See supra* notes 37–38 and accompanying text.

conjunction with off-label promotion, then the manufacturer's truthful statements used in the promotion can show the intent to conspire to sell drugs for unapproved uses.[198] In such situations, the actus reus is a gift, not speech, so there is no First Amendment issue. The speech shows that off-label promotion made the drug misbranded for lacking adequate directions for use.[199] The same speech also serves as the mens rea to explain why the gift was given.

Other evidence should also be sufficient to be the actus reus. The key is that the government must find evidence of a nonspeech act and present it at trial to avoid restricting speech based on its speaker and content.[200] For example, when a pharmaceutical representative emphasizes the benefits of off-label uses to a physician, evidence that the representative is paid on a commission basis for sales to the targeted doctor could be the actus reus for a conspiracy. This is still a circumstances-of-sale argument, but now there is evidence of a conspiracy besides speech.

Without evidence other than speech that shows a conspiracy to sell a misbranded drug, a drug company representative speaking to a doctor about off-label uses is not a crime. The government can argue that the off-label promotion shows the intent to pay the representative for selling the drug for unapproved uses, thus providing the mens rea for a conspiracy. If the representative is paid based on sales and off-label promotion is directed toward a doctor who will potentially buy the drug for off-label uses, a jury could determine that the commission is the act effectuating a conspiracy to sell a misbranded drug. Speech is not on trial—instead, speech shows the motive for the crime and makes the drug misbranded.[201] The conspiracy, by contrast, must be proven through some act other than speech, which results in the speech not being restricted based on its speaker and content.[202]

Other potential evidence of a conspiracy could be a drug company reimbursing its representative for travel costs incurred to meet with a doctor to discuss off-label uses. The speech in off-label promotion serves as evidence of the intent to sell a drug without adequate directions for use. The actus reus for the conspiracy, however, relies on evidence other than the speaker and content of speech. The manufacturer subsidized the representative's expenses to sell a drug for unapproved uses, and the representative met with a potential purchaser of the drug and engaged in off-label promotion only after receiving this subsidy. Speech shows the motive for the subsidy while also making the drug misbranded for lacking adequate directions for use.

Other potential acts that could serve as a proper actus reus include a representative giving free samples of a drug to a doctor and the existence of a sales quota that could be met only if the representative sold drugs for off-

198. *See supra* note 182.
199. *See supra* notes 27–36 and accompanying text.
200. *See, e.g.*, *supra* notes 173, 175.
201. *See supra* note 91.
202. *See supra* note 122 and accompanying text.

label uses.[203] Once again, speech is not on trial. Speech indicates that other activities occurred as part of a conspiracy to sell drugs for off-label uses and also makes the drugs misbranded.

One common method of off-label promotion, discussions about how doctors can get reimbursed by insurance companies for off-label prescriptions,[204] likely cannot be regulated. When such discussions occur, speech is the only evidence of a conspiracy. If the government alleges a conspiracy to sell a misbranded drug based on such a conversation, then the actus reus of the conspiracy must be speech—no other evidence to support a conspiracy exists. The insurance reimbursement to the doctor is an act, but it is performed by the doctor, not the drug company or its representative. The representative only spoke, so he or she would be alleged to be part of a conspiracy because of his or her speech. In effect, speech would be criminalized—speaking to a doctor about insurance reimbursement would result in criminal liability, even if the representative did not perform any act as part of a conspiracy. In a situation like this, the government must find evidence of some act on the representative's part to support his or her role in a conspiracy. If it does not, then mere discussions of insurance reimbursement for off-label uses between a pharmaceutical representative and a doctor would always result in criminal liability. This is the type of content- and speaker-based restriction on speech that *Sorrell* and *Caronia* hold is subject to *Central Hudson* scrutiny.

This analysis could lead drug manufacturers and their representatives to attempt to conceal all evidence of a conspiracy or to ensure that off-label promotion occurs only through speech. In effect, the FDA would not be able to regulate off-label promotion when it consists of truthful, nonmisleading speech. Based on *Sorrell* and *Caronia*, however, the government *must* introduce evidence other than speech at trial to prove a conspiracy to introduce a misbranded drug into interstate commerce. The government cannot restrict truthful, nonmisleading speech based on its speaker and content. Thus, the intended use-regulation must serve as an evidentiary tool and cannot be used to convict one of a misbranding crime based solely on truthful, nonmisleading speech. While *Caronia* and *Sorrell* may lead to off-label promotion effectively being beyond regulation if a drug company and its representatives conceal all nonspeech evidence of a conspiracy, the amended intended-use regulation can be used in the appropriate off-label promotion cases. Using the rule to regulate off-label promotion is constitutional, even when the promotion consists of truthful, nonmisleading speech, as long as the government has evidence other than speech of a conspiracy to introduce a misbranded drug into interstate commerce.

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203. *Off-Label Marketing of Medicines in the US Is Rife but Difficult to Control*, PUB. LIBR. SCI. (Apr. 5, 2011), https://www.eurekalert.org/pub_releases/2011-04/plos-omo040111.php [https://perma.cc/995P-88WK].

204. *Id.*

CONCLUSION

The First Amendment does not prevent the FDA from regulating the truthful, nonmisleading speech commonly used in off-label drug promotion. It has historically used the intended-use regulation to police such promotion, and it can continue to do so even after *Caronia* and *Sorrell*. While its ability to regulate in this manner is not absolute, the First Amendment and the intended-use regulation give the FDA wide leeway to use speech as evidence in an intended-use case as long as speech is not the sole evidence of a misbranding crime. Given the prevalence and legality of off-label drug usage, as well as the monetary incentives to promote drugs for unapproved uses, the FDA should use the amended regulation to ensure that consumers are prescribed drugs only when it is safe and effective to do so.